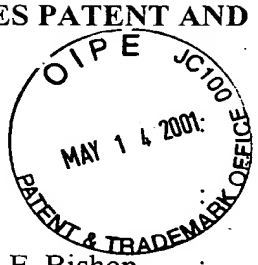
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE #12



In re:	U.S. Patent 5,889,052	
Issued:	March 30, 1999	BOX: Patent Extension
Inventors:	Peter G. Klimko, John E. Bishop, Verney L. Sallee, Paul W. Zinke	
For:	USE OF CLOPROSTENOL AND FLUPROSTENOL ANALOGUES TO: TREAT GLAUCOMA AND OCULAR HYPERTENSION	
Assignee:	Alcon Laboratories, Inc. Fort Worth, Texas	

Commissioner of Patents and Trademarks
Washington, D.C. 20231

APPLICATION FOR EXTENSION OF TERM UNDER 35 U.S.C. §156

SIR:

Applicant, Alcon Laboratories, Inc., a corporation organized and existing under and by virtue of the laws of Delaware, and having a principal place of business at 6201 South Freeway, Fort Worth, Texas 76134-2099 represents that it is the assignee of the entire interest in and to letters patent of the United States No. 5,889,052 granted to Peter G. Klimko, John E. Bishop, Verney L. Sallee and Paul W. Zinke on March 30, 1999, for "Use of Cloprostenol and Fluprostenol Analogues to Treat Glaucoma and Ocular Hypertension". An assignment of said patent was executed in the name of Alcon Laboratories, Inc. and was recorded in the U.S. Patent and Trademark Office on Reel 7143, Frame 0817 and Reel 8467, Frame 0681.

The active ingredient of TRAVATAN™ is travoprost which falls within the ambit of the claims of U.S. Patent 5,889,052. Alcon Laboratories, Inc. has been granted approval by the Food and Drug Administration for commercial marketing or use of TRAVATAN™.

Applicant, acting through its duly authorized attorney, hereby submits this application for extension of patent term under 35 U.S.C. §156 by providing the following information

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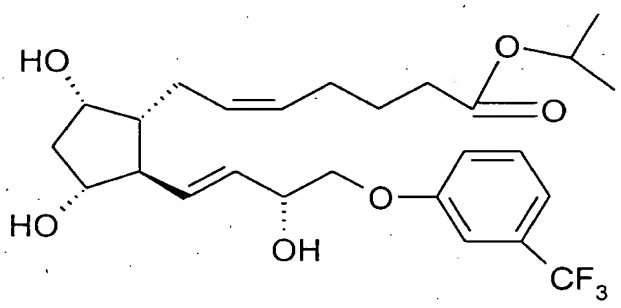
required by the rules promulgated by the U.S. Patent and Trademark Office (37 C.F.R. §1.710-1.785). For the convenience of the U.S. Patent and Trademark Office, the information presented in this application is in a format which follows the requirements of 37 C.F.R. §1.740.

(1) TRAVATAN™ contains, as the active ingredient travoprost ($C_{26}H_{35}F_3O_6$), whose chemical name is [1R-[1α(Z),2β(1E,3R*),3α,5α]-7-[3,5-Dihydroxy-2-[3-hydroxy-4-[3-(trifluoromethyl)phenoxy]-1-butenyl]cyclopentyl]-5-heptenoic acid, 1-methylethyl ester; or (Z)-7-[(1R,2R,3R,5S)-3,5-Dihydroxy-2-[(1E,3R)-3-hydroxy-4-[(α,α,α-trifluoro-*m*-isopropyl-tolyl)oxy]-1-butenyl]cyclopentyl]-5-heptenoate. Travoprost has the CAS registry number 157283-68-6 and the following structural formula



(2) The approved product, TRAVATAN™, was subject to regulatory review under the Federal Food, Drug and Cosmetic Act Section 505 (21 U.S.C. §355).

(3) The approved product, TRAVATAN™, received permission for commercial marketing or use under Section 505 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. §355) on March 16, 2001 (NDA-21-257).

(4) The only active ingredient in TRAVATAN™ is travoprost which had not been approved for commercial marketing or use under Section 505 or any other section of the Federal Food, Drug and Cosmetic Act prior to the approval of NDA-21-257 by the Food and Drug Administration. It has also not been previously approved for commercial marketing or use under the Public Health Act of the Virus-Serum-Toxin Act.

(5) This application for extension of patent term under 35 U.S.C. 156 is being submitted within the permitted 60 day period pursuant to 37 C.F.R. §1.720(f), which period will expire May 15, 2001.

(6) The complete identification of the patent for which extension is being sought

is as follows:

Inventors:	Peter G. Klimko, John E. Bishop, Verney L. Sallee and Paul W. Zinke
Patent Number:	5,889,052
Issue Date:	March 30, 1999
Expiration Date:	August 3, 2013

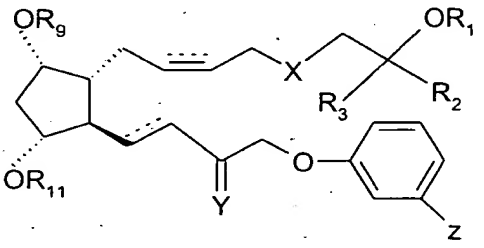
(7) See "Attachment A" for a complete copy of the patent identified in paragraph (6) hereof.

(8) No certificate of correction, receipt of maintenance fee payment or re-examination certificate has been issued with regard to U.S. Patent 5,889,052. Attached as "Attachment B" is a copy of a terminal disclaimer filed in US 5,889,052 which disclaims that portion of the patent term which extends beyond the expiration date of US patent Nos. 5,510,383 and 5,665,773, both of which expire August 3, 2013.

(9) U.S. Patent 5,889,052 claims the approved product TRAVATAN™ and methods of use thereof. Specifically, compositions containing the active ingredient travoprost and methods of using such compositions are covered under claims 1, 2, 3, 4, 5, 9-16, and 20-22 which follow:

What is claimed is:

1. A method of treating glaucoma and ocular hypertension which comprises topically administering to the affected eye a composition comprising a therapeutically effective amount of a compound having the absolute stereochemical structure of the following formula (IV), and being substantially free of the enantiomer of said compound:



(IV)

wherein

R_1 = H; C_1-C_{12} straight-chain or branched alkyl; C_1-C_{12} straight-chain or branched acyl; C_3-C_3 cycloalkyl; or a cationic salt moiety;

R_2, R_3 = H, or C_1-C_5 straight-chain or branched alkyl; or R_2 and R_3 taken together may represent O;

X = O, S, or CH_2;

---- represents any combination of a single bond, or a cis or trans double bond for the alpha (upper) chain; and a single bond or trans double bond for the omega (lower) chain;

R_9 = H, C_1-C_{10} straight-chain or branched alkyl, or C_1-C_{10} straight-chain or branched acyl;

R_{11} = H, C_1-C_{10} straight-chain or branched alkyl, or C_1-C_{10} straight-chain or branched acyl;

Y = O; or H and OR_{15} in either configuration wherein R_{15} = H, C_1-C_{10} straightchain or branched alkyl, or C_1-C_{10} straight-chain or branched acyl; and

Z = Cl or CF_3;

with the proviso that when R_2 and R_3 taken together represent O, then $R_1 \neq C_1$-C_{12} straight-chain or branched acyl; and when R_2=R_3=H, then $R_1 \neq$ a cationic salt moiety; and

with the further proviso that the following compound be excluded:

cyclopentane heptenol-5-cis-2-(3-αhydroxy-4-m-chlorophenoxy-1-transbutenyl)-3,5 dihydroxy, [1_α, 2_β, 3_α, 5_α].

2. The method of claim 1, wherein for the compound (IV):

R_2, R_3 taken together represent O;

X = CH_2;

---- represents a cis double bond for the alpha (upper) chain and a trans double bond for the omega (lower) chain;

R_9 and R_{11} = H; and

Y = OH in the alpha configuration and H in the beta configuration.

3. The method of claim 2, wherein for the compound (IV): Z=CF_3.

4. The method of claim 1, wherein: R_2 = R_3 =H, or R_2 and R_3 taken together represent O; X=O or CH_2; R_9=R_{11}=H; Y=H and OR_{15}; and R_{15}=H.

5. The method of claim 4, wherein: R_1=H, C_1-C_{12} straight chain or branched alkyl

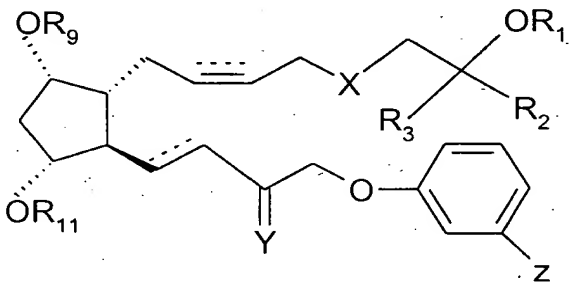
or cationic salt moiety; and R_2 and R_3 taken together represent O.

9. The method of claim 1, wherein between about 0.01 and about 1000 μg/eye of the compound is administered.

10. The method of claim 9, wherein between about 0.1 and about 100 μg/eye of the compound is administered.

11. The method of claim 10, wherein between about 0.1 and about 10 μg/eye of the compound is administered.

12. A topical ophthalmic composition for the treatment of glaucoma and ocular hypertension comprising an ophthalmically acceptable carrier and a therapeutically effective amount of a compound having the absolute stereochemical structure of the following formula (IV), and being substantially free of the enantiomer of said compound:



(IV)

wherein

R_1 = H; C_1-C_{12} straight-chain or branched alkyl; C_1-C_{12} straight-chain or branched acyl; C_3-C_8 cycloalkyl; or a cationic salt moiety;

R_2, R_3 = H, or C_1-C_5 straight-chain or branched alkyl; or R_2 and R_3 taken together may represent O;

X = O, S, or CH_2;

---- represents any combination of a single bond, or a cis or trans double bond for the alpha (upper) chain; and a single bond or trans double bond for the omega (lower) chain;

R_9 = H, C_1-C_{10} straight-chain or branched alkyl, or C_1-C_{10} straight-chain or branched acyl;

R_{11} = H, C_1-C_{10} straight-chain or branched alkyl, or C_1-C_{10} straight-chain or branched acyl;

Y = O; or H and OR_{15} in either configuration wherein R_{15} = H, C_1-C_{10} straight-chain or branched alkyl, or C_1-C_{10} straight-chain or branched acyl; and

Z = Cl or CF_3;

with the proviso that when R_2 and R_3 taken together represent O, then $R_1 \neq C_1$-C_{12} straight-chain or branched acyl; and when R_2=R_3=H, then $R_1 \neq$ a cationic salt moiety; and

with the further proviso that the following compound be excluded:

cyclopentane heptenol-5-cis-2-(3-μhydroxy4-m-chlorophenoxy-l1-transbutenyl)-3,5 dihydroxy, [1_α, 2_β, 3_α, 5_α].

13. The composition of claim 12, wherein for the compound (IV):

R_2, R_3 taken together represent O;

X = CH_2;

---- represents a cis double bond for the alpha (upper) chain and a trans double bond for the omega (lower) chain;

R_9 and R_{11} = H; and

Y = OH in the alpha configuration and H in the beta configuration.

14. The composition of claim 13, wherein for the compound (IV): Z=CF_3.

15. The composition of claim 12, wherein: R_2 = R_3 =H, or R_2 and R_3 taken together represent O; X=O or CH_2; R_9=R_{11}=H; Y=H and OR_{15}; and R_{15}=H.

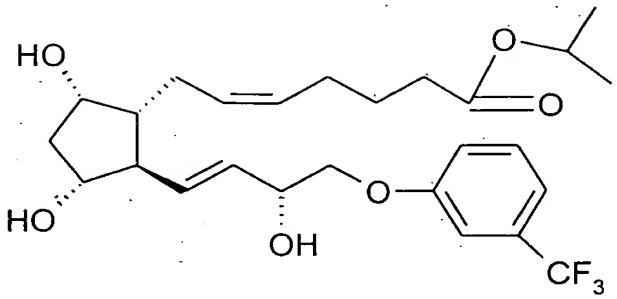
16. The composition of claim 15, wherein: R_1=H, C_1-C_{12} straight chain or branched alkyl, or cationic salt moiety; and R_2 and R_3 taken together represent O.

20. The composition of claim 12, wherein the concentration of the compound of formula (IV) is between about 0.0003 and about 0.3 wt%.

21. The composition of claim 20, wherein the concentration of the compound of formula (IV) is between about 0.0003 and about 0.3 wt%.

22. The composition of claim 21, wherein the concentration of the compound of formula (IV) is between about 0.003 and about 0.03 wt%.

Travoprost, has the following structural formula



This structure falls within the scope of claims 1 and 12, wherein R_1 is isopropyl; R_2 and R_3 together are O; X is CH_2, Z is CF_3; Y is α-OR_{15} and β-H; R_9, R_{11} and R_{15} are each H; and ---- is a cis double bond in the alpha (upper) chain and is a trans double bond in the omega (lower) chain.

Travoprost falls within the scope of claims 2 and 13 because R_2 and R_3 together are O; X is CH_2; and Y is α-OH and β-H.

Travoprost falls within the scope of claims 3 and 14 because Z is CF_3.

Travoprost falls within the scope of claims 4 and 15 because R_2 and R_3 together are O, X is CH_2; R_9, R_{11} and R_{15} are each H; and Y is H and OR_{15}.

Travoprost falls within the scope of claims 5 and 16 because R_1 is isopropyl and R_2 and R_3 together are O.

Claims 9-11 each encompass use of the product TRAVATAN™ since the concentration of the active ingredient of TRAVATAN™ (travoprost) is 40 µg/ml, and, thus, TRAVATAN™ can be used to administer travoprost in an amount of between about 0.01 and about 1000 µg/eye, about 0.1 and about 100 µg/eye and about 0.1 and about 10 µg/eye, respectively.

Claims 20-22 encompass the product TRAVATAN™ since compositions containing the active ingredient of TRAVATAN™ (travoprost) are within the scope of claim 12 and the concentration of travoprost in TRAVATAN™ is 0.004 wt%.

(10) The relevant dates and information pursuant to 35 U.S.C. §156(g) to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

The Investigational New Drug Application (IND-51.000) for travoprost was filed **June 28, 1996** and became effective on **July 28, 1996.** The New Drug Application (NDA-21-257) for TRAVATAN™ was initially submitted to the FDA on **July 7, 2000**, and approved on **March 16, 2001.**

(11) A brief description of the activities undertaken by Applicant during the applicable regulatory review period is attached hereto as "Attachment C" and is a chronological synopsis of the major communications between Applicant and the FDA from **June 28, 1996 to March 16, 2001.**

(12) Applicant is of the opinion that U.S. Patent 5,889,052 is eligible for extension under 35 U.S.C. §156 because it satisfies all of the requirements for such extension as follows:

(a) 35 U.S.C. §156(a); 37 C.F.R. §1.720(a)

U.S. Patent 5,889,052 claims a product;

(b) 35 U.S.C. §156(a)(1); 37 C.F.R. §1.720(g)

The term of U.S. Patent 5,889,052 has not expired before submission of this application;

(c) 35 U.S.C. §156(a)(2); 37 C.F.R. §1.720(b)

The term of U.S. Patent 5,889,052 has never been extended;

(d) 35 U.S.C. §156(a)(3); 37 C.F.R. §1.730

The application for extension is submitted by the authorized agent or the owner of record in accordance with the requirement of 35 U.S.C. §156(d) and the rules of the U.S. Patent and Trademark Office;

(e) 35 U.S.C. §156(a)(4); 37 C.F.R. §1.720(d)

The product TRAVTAN™ has been subject to a regulatory review period as defined in 35 U.S.C. §156(g) before its commercial marketing or use;

(f) 35 U.S.C. §156(a)(5)(A); 37 C.F.R. §1.720(e)(i)

The commercial marketing or use of the product TRAVATAN™ after the regulatory review period is the first permitted commercial marketing or use of the product under the provision of the Federal Food, Drug and Cosmetics Act (21 U.S.C. 360) under which such regulatory review period occurred.

(g) 35 U.S.C. §156(c)(4); 37 C.F.R. §1.720(h)

No other patent has been extended for the same regulatory review period for the product TRAVATAN™.

(h) 35 U.S.C. §156(d)(1); 37 C.F.R. §1.720(f)

The application is submitted within the permitted 60 day period beginning on the date the product first received permission for commercial marketing or use.

(i) The length of extension of the patent term of U.S. Patent 5,889,052 claimed by applicant is **484** days. The length of extension was determined pursuant to 37

C.F.R. §1.775 as follows:

(i) The regulatory review period under 35 U.S.C. §156(g)(1)(B) began **July 28, 1996** and ended **March 16, 2001**, which is a total of **1692** days which is the sum of (ii) and (iii) below;

(ii) The period of review under 35 U.S.C. §156(g)(1)(B)(i), the IND period, began on **July 28, 1996** and ended on **July 7, 2000**, which is **1440** days.

(iii) The period of review under 35 U.S.C. §156(g)(1)(B)(ii), the "Application Period," began on **July 7, 2000** and ended **March 16, 2001**, which is **252** days.

(j) The regulatory review period upon which the period of extension is calculated is the entire regulatory review period as determined in subparagraph 12(i)(i) (1692 days) less

(i) The number of days in the regulatory review period which were on or before the date on which the patent issued (March 30, 1999), which is **975** days, and

(ii) The number of days during which applicant did not act with due diligence, which is zero (0) days, and

(iii) One-half the number of days determined in subparagraph 12(i)(ii) after subtracting therefrom the number of days of subparagraphs (12)(j)(i) and (j)(ii) (976 days in total), or **232** days,

which totals **484** days.

(k) The number of days as determined in subparagraph 12(j)(iii) (484 days) when added to the original term of the patent would result in the date **November 30, 2014.**

(l) Fourteen (14 years) when added to the date of the NDA approval (March 16, 2001) would result in the date **March 16, 2015.**

(m) The earliest date as determined in paragraphs 12(k) and 12(l) is **November 30, 2014.**

(n) The issuance of the original exemption occurred after September 24, 1984.

Five (5) years when added to the original expiration date of the patent (August 3, 2013) would result in the date **August 3, 2018.**

(o) The earlier date as determined in paragraphs (m) and (n) is **November 30, 2014.**

Therefore, the length of extension of patent term claimed by applicant is **484 days or one (1) year and 119 days.**

(13) Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any Information which is material to the determination of entitlement to the extension sought.

(14) The prescribed fee pursuant to 37 C.F.R. §1.20(j) for receiving and acting upon this application is to be charged to the Deposit Account of Applicant as authorized in the attached letter, which is submitted in triplicate.

(15) All inquiries and correspondence relating to this application are to be directed to the undersigned.

Two copies of these application papers, certified as such, are being submitted herewith.

Respectfully submitted

Barry L. Copeland, Esq.
Registration No. 34,801
Attorney for Applicant(s)
Assistant General Counsel

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Filed: 5/14/01

DAPetition
9200/1611

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent 5,889,052

Issued: March 30, 1999

BOX: Patent Extension

Inventors: Peter G. Klimko, John E. Bishop, Verney L. Sallee, Paul W. Zinke

For: USE OF CLOPROSTENOL AND FLUPROSTENOL ANALOGUES TO: TREAT GLAUCOMA AND OCULAR HYPERTENSION

Assignee: Alcon Laboratories, Inc. Fort Worth, Texas

TRANSMITTAL LETTER

Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

SIR:

Being filed herewith are the following papers:

1. Application for Extension of Patent Term Under 35 U.S.C. §156;
2. Attachment A (copy of U.S. Patent No. 5,889,052);
3. Attachment B (copy of Terminal Disclaimer filed in U.S. 5,889,052);
4. Attachment C (brief description under 37 C.F.R. §1.755); and
5. Two certified duplicates of all of the above.

Authorization is hereby granted to charge the fee of $1,120.00 under 37 C.F.R. §1.21(j) for filing of an application for extension of the term of a patent to Deposit Account

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No. 01-0682. Two copies of this page are attached for this purpose. Authorization is also granted to charge any other fee which might be necessary in conjunction with this filing.

Respectfully submitted,

Barry L. Copeland, Esq.
Registration No. 34,801
Attorney for Applicant(s)
Assistant General Counsel

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Filed: 5/14/01

ATTACHMENT A

US005889052A

United States Patent [19]

Klimko et al.

[11] **Patent Number: 5,889,052**

[45] **Date of Patent: *Mar. 30, 1999**

[54] **USE OF CLOPROSTENOL AND FLUPROSTENOL ANALOGUES TO TREAT GLAUCOMA AND OCULAR HYPERTENSION**

[75] Inventors: **Peter G. Klimko**, Fort Worth, Tex.; **John E. Bishop**, Groton, Mass.; **Verney L. Sallee**, Burleson; **Paul W. Zinke**, Fort Worth, both of Tex.

[73] Assignee: **Alcon Laboraties, Inc.**, Fort Worth, Tex.

[*] Notice: The term of this patent shall not extend beyond the expiration date of Pat. Nos. 5,510,383, and 5,665,773.

[21] Appl. No.: **917,795**

[22] Filed: **Aug. 21, 1997**

Related U.S. Application Data

[63] Continuation of Ser. No. 769,293, Dec. 18, 1996, Pat. No. 5,665,773, which is a continuation of Ser. No. 280,681, Jul. 26, 1994, abandoned, which is a continuation-in-part of Ser. No. 101,598, Aug. 3, 1993, Pat. No. 5,510,383.

[51] **Int. Cl.**[6] **A61K 31/557**

[52] **U.S. Cl.** **514/530**; 514/573

[58] **Field of Search** 514/530, 573

[56] **References Cited**

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Primary Examiner—Richard L. Raymond

Attorney, Agent, or Firm—Barry L. Copeland

[57] **ABSTRACT**

Disclosed is the use of cloprostenol and fluprostenol analogues for the treatment of glaucoma and ocular hypertension. Also disclosed are ophthalmic compositions comprising said compounds.

22 Claims, No Drawings

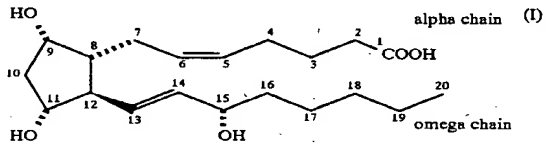
USE OF CLOPROSTENOL AND FLUPROSTENOL ANALOGUES TO TREAT GLAUCOMA AND OCULAR HYPERTENSION

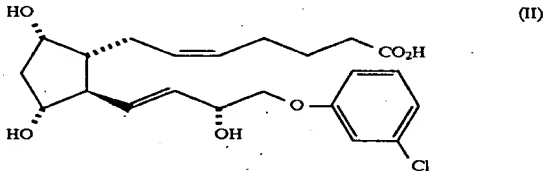
The present application is a continuation of U.S. patent application Ser. No. 08/769,293, filed Dec. 18, 1996, now U.S. Pat. No. 5,665,773, which is a continuation of U.S. patent application Ser. No. 08/280,681, filed Jul. 26, 1994, now abandoned, which is a continuation-in-part of U.S. patent application Ser. No. 08/101,598 filed Aug. 3, 1993 now U.S. Pat. No. 5,510,383.

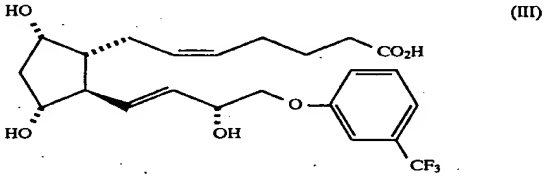
BACKGROUND OF THE INVENTION

The present invention relates to the treatment of glaucoma and ocular hypertension. In particular, the present invention relates to the use of cloprostenol and fluprostenol analogues for the treatment of glaucoma and ocular hypertension.

Cloprostenol and fluprostenol, both known compounds, are synthetic analogues of $PGF_{2\alpha}$, a naturally-occurring F-series prostaglandin (PG). Structures for $PGF_{2\alpha}$ (I), cloprostenol (II), and fluprostenol (III), are shown below:







The chemical name for cloprostenol is 16-(3-chlorophenoxy)-17,18,19,20-tetranor $PGF_{2\alpha}$. Monograph No. 2397 (page 375) of *The Merck Index*, 11th Edition (1989) is incorporated herein by reference to the extent that it describes the preparation and known pharmacological profiles of cloprostenol. Fluprostenol has the chemical name 16-(3-trifluoromethylphenoxy)-17,18,19,20-tetranor $PGF_{2\alpha}$. Monograph No. 4121 (pages 656–657) of *The Merck Index*, 11th Edition (1989) is incorporated herein by reference to the extent that it describes the preparation and known pharmacological profiles of fluprostenol. Cloprostenol and fluprostenol are 16-aryloxy PGs and, in addition to the substituted aromatic ring, differ from the natural product $PGF_{2\alpha}$, in that an oxygen atom is embedded within the lower (omega) chain. This oxygen interruption forms an ether functionality.

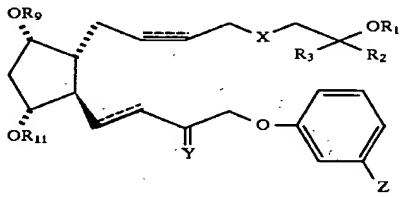
Naturally-occurring prostaglandins are known to lower intraocular pressure (IOP) after topical ocular instillation, but generally cause inflammation, as well as surface irritation characterized by conjunctival hyperemia and edema. Many synthetic prostaglandins have been observed to lower intraocular pressure, but such compounds also produce the aforementioned side effects which severely restrict clinical utility.

SUMMARY OF THE INVENTION

It has now been unexpectedly found that certain novel cloprostenol and fluprostenol analogues are useful in treating glaucoma and ocular hypertension. In particular, topical application of ophthalmic compositions comprising these novel cloprostenol and fluprostenol analogues result in significant IOP reduction.

DETAILED DESCRIPTION OF THE INVENTION

The compounds useful in the present invention have the following general formula:



(IV)

wherein:

R_1=H; C_1–C_{12} straight-chain or branched alkyl; C_1–C_{12} straight-chain or branched acyl; C_3–C_8 cycloalkyl; or a cationic salt moiety;

R_2, R_3 =H, or C_1–C_5 straight-chain or branched alkyl; or R_2 and R_3 taken together may represent O;

X=O, S, or CH_2;

⁻⁻⁻ represents any combination of a single bond, or a cis or trans double bond for the alpha (upper) chain; and a single bond or trans double bond for the omega (lower) chain;

R_9=H, C_1–C_{10} straight-chain or branched alkyl, or C_1–C_{10} straight-chain or branched acyl;

R_{11} =H, C_1–C_{10} straight-chain or branched alkyl, or C_1–C_{10} straight-chain or branched acyl;

Y=O; or H and OR_{15} in either configuration wherein R_{15}=H. C_1–C_{10} straight-chain or branched alkyl, or C_1–C_{10} straight-chain or branched acyl; and

Z=Cl or CF_3;

with the proviso that when R_2 and R_3 taken together represent O, then R_1≠C_1–C_{12} straight-chain or branched acyl; and when R_2 =R_3 =H, then R_1≠a cationic salt moiety.

As used herein, the term "cationic salt moiety" includes alkali and alkaline earth metal salts as well as ammonium salts.

Preferred compounds include the 3-oxa form of cloprostenol isopropyl ester (Table, 1, compound 5), 13,14-dihydrofluprostenol isopropyl ester (compound 6), cloprostenol-1-ol (compound 7), and 13,14-dihydrocloprostenol-1-ol pivaloate (compound 8).

The compounds of formula (IV) are useful in lowering intraocular pressure and thus are useful in the treatment of glaucoma. The preferred route of administration is topical. The dosage range for topical administration is generally between about 0.01 and about 1000 micrograms per eye (μg/eye), preferably between about 0.1 and about 100

μg/eye, and most preferably between about 1 and 10 μg/eye. The compounds of the present invention can be administered as solutions, suspensions, or emulsions (dispersions) in a suitable ophthalmic vehicle.

In forming compositions for topical administration, the compounds of the present invention are generally formulated as between about 0.00003 to about 3 percent by weight (wt %) solutions in water at a pH between 4.5 to 8.0. The compounds are preferably formulated as between about 0.0003 to about 0.3 wt % and, most preferably, between about 0.003 and about 0.03 wt %. While the precise regimen is left to the discretion of the clinician, it is recommended that the resulting solution be topically applied by placing one drop in each eye one or two times a day.

Other ingredients which may be desirable to use in the ophthalmic preparations of the present invention include preservatives, co-solvents and viscosity building agents.

Antimicrobial Preservatives:

Ophthalmic products are typically packaged in multidose form, which generally require the addition of preservatives to prevent microbial contamination during use. Suitable preservatives include: benzalkonium chloride, thimerosal, chlorobutanol, methyl paraben, propyl paraben, phenylethyl alcohol, edetate disodium, sorbic acid, ONAMER M®, or other agents known to those skilled in the art. Such preservatives are typically employed at a concentration between about 0.001% and about 1.0% by weight.

Co-Solvents:

Prostaglandins, and particularly ester derivatives, typically have limited solubility in water and therefore may require a surfactant or other appropriate co-solvent in the composition. Such co-solvents include: Polysorbate 20, 60 and 80; Pluronic F-68, F-84 and P-103; Tyloxapol®; Cremophor® EL; sodium dodecyl sulfate; glycerol; PEG 400; propylene glycol; cyclodextrins; or other agents known to those skilled in the art. Such co-solvents are typically employed at a concentration between about 0.01% and about 2% by weight.

Viscosity Agents:

Viscosity greater than that of simple aqueous solutions may be desirable to increase ocular absorption of the active compound, to decrease variability in dispensing the formulations, to decrease physical separation of components of a suspension or emulsion of formulation and/or otherwise to improve the ophthalmic formulation. Such viscosity building agents include, for example, polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxy propyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxy propyl cellulose or other agents known to those skilled in the art. Such agents are typically employed at a concentration between about 0.01% and about 2% by weight.

The following Examples 1–4 describe the synthesis of compounds 5–8 (Table 1). These syntheses are representative in nature and are not intended to be limiting. Other compounds of formula (IV) may be prepared using analogous techniques known to those skilled in the art.

TABLE 1

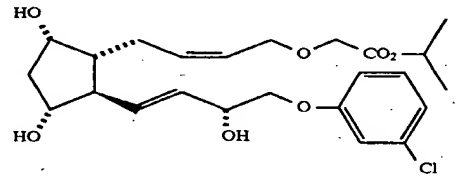
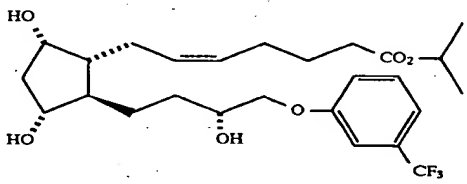
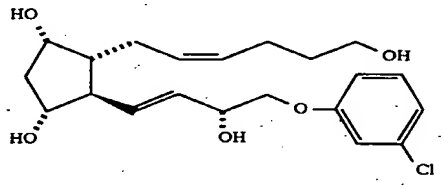
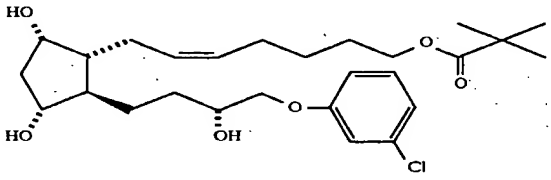
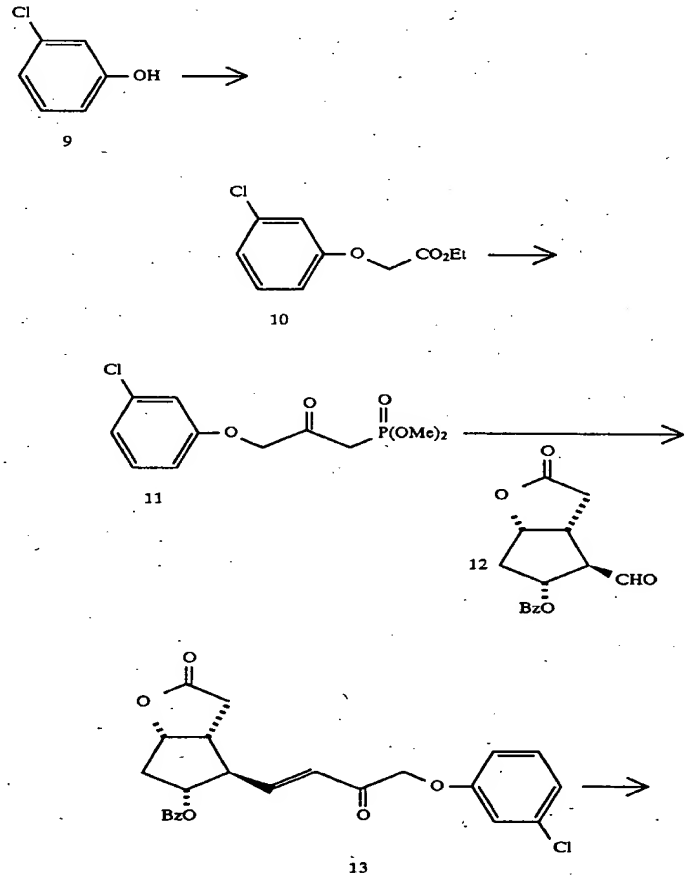
COMPOUND NAME	COMPOUND STRUCTURE
5 3-oxacloprostenol isopropyl ester	
6 13,14-dihydrofluprostenol isopropyl ester	
7 cloprostenol-1-ol	

TABLE 1-continued

	COMPOUND NAME	COMPOUND STRUCTURE
8	13,14-dihydrocloprostenol-1-ol pivaloate	

In the examples below, the following standard abbreviations are used: g=grams (mg=milligrams); mol=moles (mmol=millimoles); mol %=mole percent; mL=milliliters; mm Hg=millimeters of mercury; mp=melting point; bp=boiling point; h=hours; and min=minutes. In addition, "NMR" refers to nuclear magnetic resonance spectroscopy and "Cl MS" refers to chemical ionization mass spectrometry.

EXAMPLE 1: Synthesis of 3-Oxacloprostenol (5)



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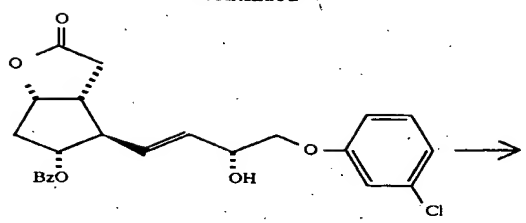

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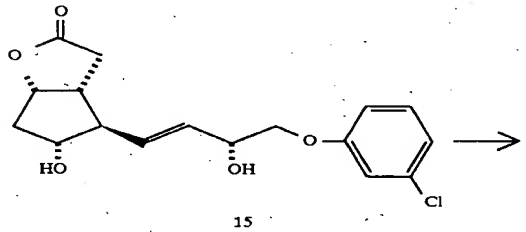

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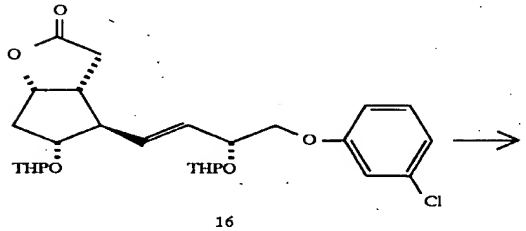

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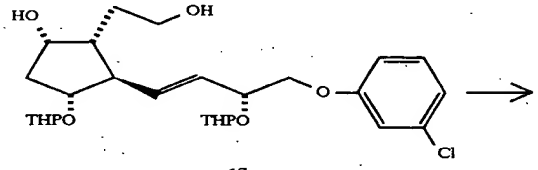

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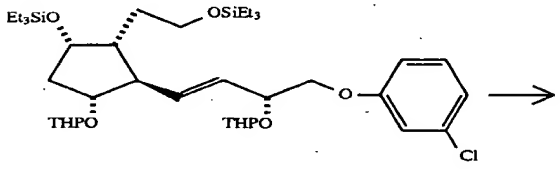

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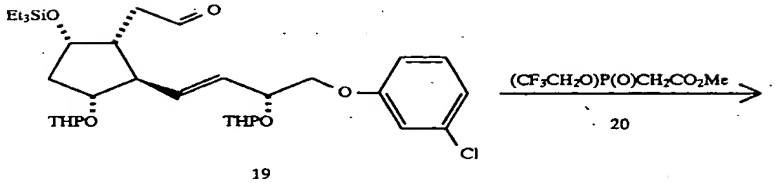

19 20

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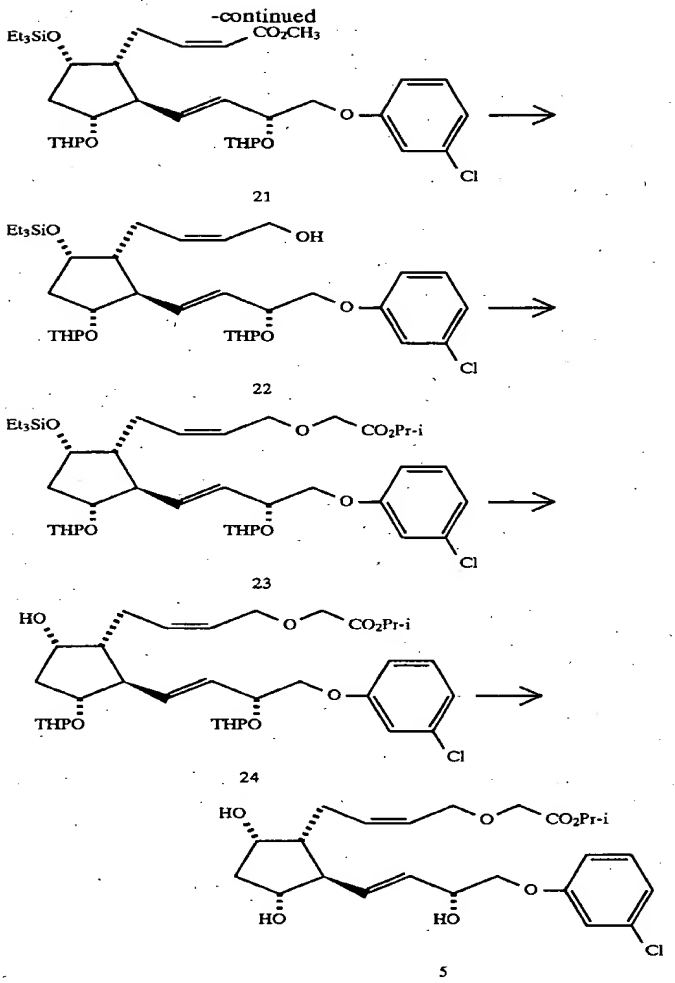


A: Ethyl (3-chlorophenoxy)acetate (10)

Acetone (320 ml), 75 g (450 mmol) of ethyl bromoacetate, and 40.0 g (310 mmol) of 3-chlorophenol were mixed together, then 69.8 g (505 mmol) of potassium carbonate was added. The mixture was mechanically stirred and heated to reflux for 4 h, and after cooling to room temperature, was poured into 350 mL of ethyl acetate. To this was then cautiously added 400 mL of 1M HCl, taking care to avoid excess foaming. The layers were separated and the aqueous layer was extracted with portions of ethyl acetate (3×200 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated, and the resulting solid was recrystallized from hexane to afford 58 g (87%) of 10 as a white solid, m.p.=39°–40° C. ^1H NMR δ 7.20–7.08 (m, 1 H), 6.95–6.82 (m, 2 H), 6.75–6.70 (m, 1 H), 4.53 (s, 2 H), 4.21 (q, J=7.2 Hz, 2 H), 1.23 (t, J=7.2 Hz, 3 H).

B: Dimethyl [3-(3-chlorophenoxy)-2-oxoprop-1 -yl] phosphonate (11)

To 20.6 g (166 mmol, 238 mol %) of dimethyl methylphosphonate in 110 mL of THF at −78° C. was added dropwise 65 mL (162 mmol, 232 mol %) of a 2.5M solution of n-BuLi in hexanes. After addition was complete, the mixture was stirred for an additional 1 h, after which 15.0 g (69.9 mmol) of aryloxyester 10 in 40 mL of THF was added dropwise. The reaction was stirred for 1 h and then quenched by the addition of 100 mL of saturated NH_4Cl. The mixture was poured into 200 mL of a 1/1 mixture of saturated NaCl/ethyl acetate, layers were separated, and the aqueous layer was further extracted with ethyl acetate (2×100 mL). Combined organic layers were dried over $MgSO_4$, filtered, and concentrated, to afford 20.5 g (100%) of 11 as a viscous oil. ^1H NMR δ 7.22 (t, J=8.1 Hz, 1 H), 7.05–6.90 (m, 2 H), 6.85–6.78 (m, 1 H), 4.72 (s, 2 H), 3.84 (s, 3 H), 3.78 (s, 3 H), 3.27 (d, J=22.8 Hz, 2 H).

C: (3aR, 4R, 5R, 6aS)-5-(Benzoyloxy)-4-[(E)-4-(3-chlorophenoxy)-3-oxo-1-butenyl]hexahydro-2H-cyclopenta [b]furan-2-one (13)

Phosphonate 11 (20.5 g, 70.0 mmol), 2.6 g (62 mmol) of LiCl, and 200 mL of THF were mixed together at 0° C. and 6.10 g (60.4 mmol) of NEt_3 was added. Aldehyde 12 (14.0

g, 51.1 mmol) dissolved in 50 mL of CH_2Cl_2 was then added dropwise. After 1 h, the reaction was poured into 200 mL of a 1/1 mixture of saturated NH_4Cl/ethyl acetate, the layers were separated, and the aqueous layer was extracted with ethyl acetate (2×100 mL). Combined organic layers were dried over $MgSO_4$, filtered, concentrated, and the residue was chromatographed on silica gel eluting with ethyl acetate/hexanes, 3/2, to afford 16.2 g (72%) of 13 as a white crystalline solid, m.p.=101.0°–102.00° C. ^1H NMR δ 8.0–7.9 (m, 2 H), 7.62–7.52 (m, 1 H), 7.50–7.38 (m, 2 H), 7.18 (t, J=8.2 Hz, 1 H), 7.0–6.82 (m, 3 H), 6.75–6.70 (m, 1 H), 6.54 (d, J=15.1 Hz, 1 H), 5.32 (q, J=6.2 Hz, 1 H), 5.12–5.05 (m, 1 H), 4.66 (s, 2 H), 3.0–2.8 (m, 3 H), 2.7–2.2 (m, 3 H).

D: (3aR, 4R, 5R, 6aS)-5-(Benzoyloxy)-4-[(E)-(3R)-4-(3-chlorophenoxy)-3-hydroxy-1 -butenyl]-hexahydro-2H-cyclopenta[b]furan-2-one (14)

To a solution of 9.70 g (22.0 mmol) of enone 13 in 60 mL of THF at −23° C. was added dropwise a solution of 11.1 g (34.6 mmol) of (-)-B-chlorodiisopino-campheylborane in 30 mL of THF. After 4 h, the reaction was quenched by the dropwise addition of 5 mL of methanol and then warmed to room temperature. After pouring into 200 mL of a 2/1 mixture of ethyl acetate/saturated NH_4Cl, the layers were separated, and the aqueous phase was extracted with ethyl acetate (2×100 mL). Combined organic layers were dried over $MgSO_4$, filtered, concentrated, and the residue was chromatographed on silica gel eluting with ethyl acetate/hexanes, 3/2, to afford 4.7 g (48%) of 14 as a white solid, m.p. 101.0°–102.5° C. ^1H NMR δ 8.05–7.95 (m, 2 H), 7.62–7.40 (m, 3 H), 7.18 (t, J=8.0 Hz, 1 H), 7.0–6.92 (m, 1 H), 6.85 (t, J=2.1 Hz, 1 H), 6.77–6.70 (m, 1 H), 5.85 (d of d, J=6.2, 15.5 Hz, 1 H), 5.72 (d of d, J=4.5, 15.5 Hz, 1 H), 5.30 (q, J=5.8 Hz, 1 H), 5.12–5.04 (m, 1 H), 4.58–4.48 (m, 1 H), 3.92 (d of d, J=3.5, 9.3 Hz, 1 H), 3.80 (d of d, J=7.3, 9.4 Hz, 1 H), 2.9–2.2 (m, 8 H).

E: (3aR, 4R, 5R, 6aS)-4-[(E)-(3R)-4-(3-Chlorophenoxy)-3-(tetrahydropyran-2-yloxy)-1-butenyl]-5-(tetrahydropyran-2-yloxy)-hexahydro-2H-cyclopenta[b]furan-2-one (16)

To a mixture of 5.1 g (11.5 mmol) of 14 in 200 mL of methanol was added 1.7 g (12 mmol) of K_2CO_3. After 1 h, the mixture was poured into 100 mL of 0.5M HCl and extracted with ethyl acetate (3×100 mL). The combined organic layers were washed successively with water (2×100 mL) and saturated NaCl (2×100 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated to afford 4.85 g of crude diol 15, which was used in the next step without further purification.

To a mixture of 4.85 9 of crude 15 and 2.4 g (28 mmol) of 3,4-dihydro-2H-pyran in 75 mL of CH_2Cl_2 at 0° C. was added 370 mg (1.9 mmol) of p-toluenesulfonic acid monohydrate. After stirring for 45 min, the reaction was poured into 40 mL of saturated $NaHCO_3$, layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2×40 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed on silica gel eluting with 40% ethyl acetate in hexanes, to afford 6.0 g (100%) of 16 as an oil. ^1H NMR ($CDCl_3$) δ (characteristic peaks only) 7.25–7.14 (m, 1 H), 6.95–6.87 (m, 2 H), 6.83–6.72 (m, 1 H), 5.8–5.4 (m, 4 H), 5.1–4.8 (m, 2 H).

F: (13E)-(9S, 11R, 15R)-11,15-Bis(tetrahydropyran-2-yloxy)-16-(3-chlorophenoxy)-2,3,4.5,6,17,18,19,20-nonanor-9-triethylsilyloxy-13-prostenol Triethylsilyl Ether (18)

To a suspension of 400 mg (10.5 mmol) of lithium aluminum hydride in 20 mL of THF at 0° C. was added dropwise a solution of 4.5 g (8.8 mmol) of lactone 16 in 20 mL of THF. After 1 h at 0° C. the mixture was cautiously poured into 100 mL of a 1/1 mixture of ice-cold saturated NH_4Cl/ethyl acetate. The layers were separated, and the aqueous layer was extracted with ethyl acetate (2×50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford 4.5 g (100%) of diol 17 which was used in the next step without further purification.

Triethylsilyl chloride (3.0 g, 20 mmol) was added to a mixture of 4.5 g (8.8 mmol) of crude 17, 40 mL of DMF, 1.85 g (27.0 mmol) of imidazole, and 310 mg (2.5 mmol) of 4-(dimethylamino)pyridine. After 2 h, the reaction was poured into 100 mL of a 1/1 mixture of ethyl acetate/saturated NH_4Cl, layers were separated, and the aqueous layer was extracted with ethyl acetate (2×25 mL). The combined organic layers were washed with water (3×25 mL), dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel eluting with 20% ethyl acetate in hexane to afford 5.2 g (80%) of 18. ^1H NMR ($CDCl_3$) δ (characteristic peaks only) 7.22–7.12 (m, 1 H), 6.95–6.88 (m, 2 H), 6.83–6.71 (m, 1 H), 5.8–5.4 (m, 4 H), 5.1–4.8 (m, 2 H), 1.0–0.85 (m, 18 H), 0.7–0.5 (m, 12 H).

G: (13E)-(9S, 11R, 15R)-11,15-Bis(tetrahydropyran-2-yloxy)-16-(3-chlorophenoxy)-2,3,4,5,6,17,18,19,20-nonanor-9-triethylsilyloxy-13-prostenal (19)

To a mixture of 1.6 g (12.6 mmol) of oxalyl chloride and 15 mL of CH_2Cl_2 at −78° C. was added dropwise a solution of 1.54 g (19.7 mmol) of DMSO in 2 mL of CH_2Cl_2. After 10 min, 4.6 g (6.2 mmol) of bissilane 18 in 8 mL of CH_2Cl_2 was added dropwise. After 95 min, 3.0 g (30 mmol) of NEt_3 was added. The mixture was then warmed to room temperature and poured into 70 mL of saturated NH_4Cl. The solution was extracted with of CH_2Cl_2 (3×70 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed on silica gel eluting with 20% ethyl acetate in hexane to afford 2.06 g (53%) of 19 as well as 1.5 g (26%) recovered 18. ^1H NMR ($CDCl_3$) δ (characteristic peaks only) 9.78 (t, J=1.4 Hz, 1 H), 7.22–7.12 (m, 1 H), 6.95–6.88 (m, 2 H), 6.83–6.71 (m, 1 H), 5.8–5.4 (m, 4 H) 5.1–4.8 (m, 2 H), 1.0–0.85 (m, 18 H), 0.7–0.5 (m, 12 H).

H: (5Z, 13E)-(9S, 11R, 15R)-11,15-Bis(tetrahydropyran-2-yloxy)-16-(3-chlorophenoxy)-2,3,4,17,18,19,20-heptanor-9-triethylsilyloxy-5,13-prostadienoic Acid Methyl Ester (21)

To a solution of 1.35 g (4.24 mmol) of phosphonate 20 and 2.60 g (9.84 mmol) of 18-crown-6 in 20 mL of THF at −78° C. was added dropwise 6.9 mL (3.45 mmol) of a 0.5M solution of potassium hexamethyldisilazane in toluene. After stirring for 15 min, a solution of 1.65 g (2.64 mmol) of aldehyde 19 in 20 mL of THF was added dropwise. One hour later, the mixture was poured into 100 mL of saturated NH_4Cl/ethyl acetate, 1/1, layers were separated, and the aqueous layer was extracted with ethyl acetate (3×30 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and the residue was chromatographed on silica gel eluting with 20% ethyl acetate in hexane to afford 1.135 g (63%) of 21. ^1H NMR ($CDCl_3$) δ (characteristic peaks only) 7.22–7.11 (m, 1 H), 6.97–6.86 (m, 2 H), 6.85–6.75 (m, 1 H), 6.4–6.2 (m, 1 H), 5.8–5.32 (m, 3 H), 3.66 (s, 3 H).

I: (5Z, 13E)-(9S, 11R, 15R)-11,15-Bis(tetrahydropyran-2-yloxy)-16-(3-chlorophenoxy)-2,3,4,17,18,19,20-heptanor-9-triethylsilyloxy-5,13-prostadien-1-ol (22)

To a solution of 850 mg (1.25 mmol) of ester 21 in 10 mL of THF at 0° C. was added 2.4 mL (3.6 mmol) of a 1.5M solution of diisobutylaluminum hydride in toluene. After 1 h, the mixture was poured into 20 mL of saturated NH_4Cl and was extracted with ethyl acetate (3×20 mL). Combined organic layers were dried over $MgSO_4$, filtered, and concentrated down to 800 mg (98%) of 22 as an oil. ^1H NMR ($CDCl_3$) δ (characteristic peaks only) 7.25–7.15 (m, 1 H), 6.97–6.90 (m, 2 H), 6.86–6.75 (m, 1 H), 5.81–5.41 (m, 4 H).

J: (5Z, 13E)-(9S, 11R, 15R)-11,15-Bis(tetrahydropyran-2-yloxy)-16-(3-chlorophenoxy)-3-oxa-17,18,19,20-tetranor-9-triethylsilyloxy-5,13-grostadienoic Acid Isopropyl Ester (23)

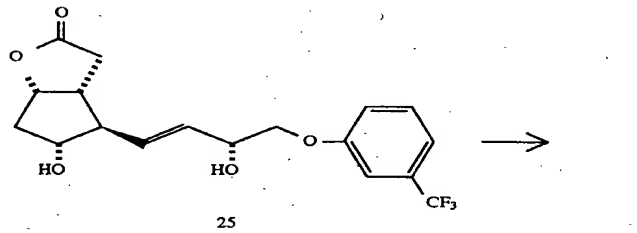
To a solution of 415 mg (6.37 mmol) of alcohol 22 in 4 mL of THF at −78° C. was added dropwise 0.35 mL (0.87 mol) of a 2.5M solution of n-BuLi in hexane. After 15 min, this solution was transferred via syringe to a −78° C. solution of 195 mg (1.08 mmol) of isopropyl bromoacetate in 2 mL of THF. The mixture was kept at −78° C. for 40 min, warmed to room temperature overnight, and then poured into 20 mL of a 1/1 mixture of saturated NH_4Cl/ethyl acetate. Layers were separated, and the aqueous layer was extracted with ethyl acetate (2×10 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated, and the residue was chromatographed on silica gel (20% ethyl acetate in hexane) to afford 242 mg (53%) of 23 as an oil. ^1H NMR ($CDCl_3$) δ (characteristic peaks only) 7.24–7.15 (m, 1 H), 6.97–6.90 (m, 2 H), 6.86–6.75 (m, 1 H), 5.81–5.41 (m, 4 H), 1.57 (d, J=5.7 Hz, 6 H).

K: (5Z, 13E)-(9S, 11R, 15R)-16-(3-Chlorophenoxy)-3-oxa-17,18,19,20-tetranor-9,11,15-trihydroxy-5,13-prostadienoic Acid Isopropyl Ester (5)

To a solution of 230 mg (0.32 mmol) of silane 23 in 5 mL of THF at room temperature was added 0.33 mL (0.33 mmol) of a 1M solution of Bu_4NF in THF. After 20 min, the reaction was poured into 4 mL of saturated NH_4Cl and was extracted with ethyl acetate (4×5 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated, and the residue was chromatographed on silica gel (ethyl acetate/hexane, 1/1), to afford 126 mg (65%) of desilylated compound 24.

To 120 mg of 24 in 5 mL of methanol was added 0.4 mL of 2M HCl. After 1 h, the mixture was added to 3 mL of saturated $NaHCO_3$, and the resulting mixture was extracted with ethyl acetate (3×8 mL). Combined organic layers were dried over $MgSO_4$, filtered, concentrated. The resulting residue was then chromatographed on silica gel eluting with ethyl acetate to afford 54 mg (56%) of 5. ^{13}C NMR ($CDCl_3$) δ 169.92 (C), 159.26 (C), 135,13 (CH), 134.95 (CH), 134.81 (C), 124.93 (CH), 121.22 (CH), 115.06 (CH), 113.08 (CH), 77.75 (CH), 72.02 (CH), 71.94 (CH_2), 70.76 (CH_2), 68.77 (CH), 67.78 (CH_2), 66.50 (CH_2), 55.46 (CH), 49.93 (CH), 42.47 (CH_2), 25.85 (CH_2), 21.75 (CH_3). Cl MS, m/z calcd. for $C_{24}H_{34}O_7Cl_1(MH^+)$, 469.1993, found 469.1993.

EXAMPLE 2: Synthesis of 13,14-Dihydrofluprostenol Isopropyl Ester



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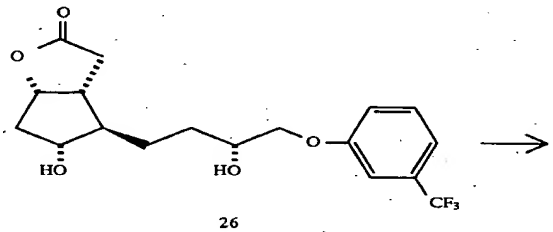

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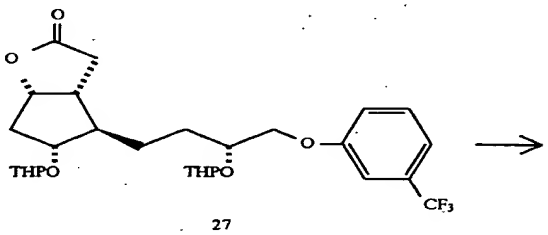

27

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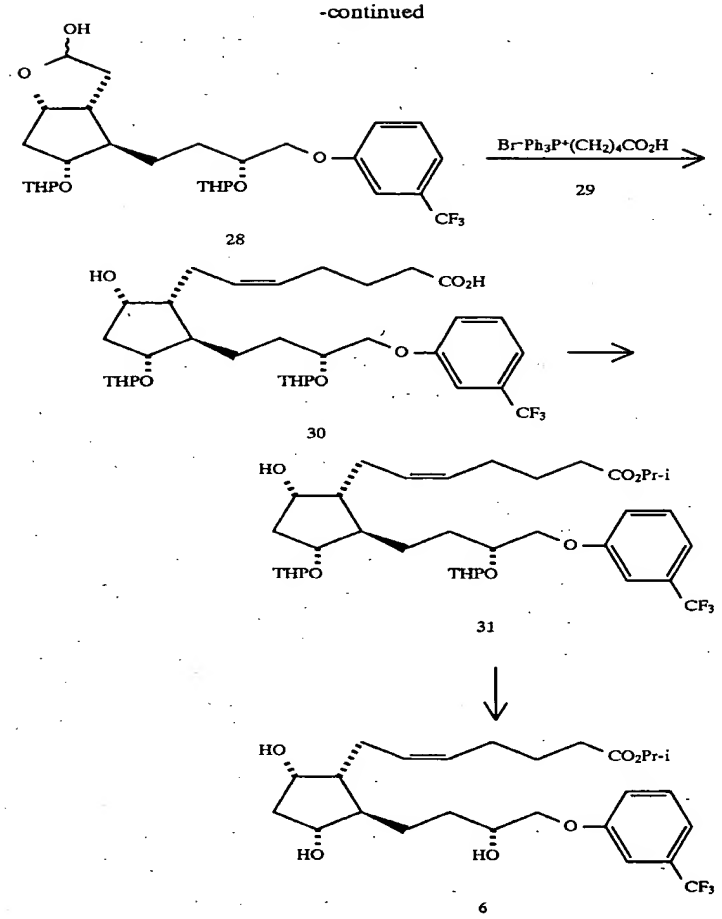


A: (3aR, 4R, 5R, 6aS)-5-Hydroxy-4-[(3R)-4-(3-trifluoromethylphenoxy)-3-hydroxy-1-butyl]-hexahydro-2H-cyclopenta[b]furan-2-one (26)

A mixture of 1.2 g (3.2 mmol) of diol 25 (for synthesis of diol 25, see U.S. Pat. No. 4,321,275) and 0.05 g of 10% (wt/wt) Pd/C in 20 mL of methanol was hydrogenated at 30 psi for 1.5 hours. After filtration through a short pad of Celite® concentration afforded 1.2 g (100%)of 26 as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.44 (m, 2 H), 7.12 (m, 2 H), 4.95 (dt, 1 H), 4.15–3.80 (m, 4 H), 2.82 (dd, J=10.8, 1 H), 2.55 (m, 2 H), 2.3 (m, 1 H), 2.1–1.3 (m, 6 H).

B: (3aR, 4R, 5R, 6aS)-5-(Tetrahydropyran-2-yloxy)-4-[(3R)-4-(3-trifluoromethylphenoxy)-3-(tetrahydropyran-2-yloxy)-1-butyl]-hexahydro-2H-cyclopenta[b]furan-2-one (27)

A mixture of 1.2 g (3.2 mmol) of diol 26 and 0.05 g of ptoluenesulfonic acid monohydrate in 100 mL of CH_2Cl_2 at 0° C. was treated with 3,4-dihydro-2H-pyran (1.1 ml, 12 mmol) and the solution was stirred for 2 h at 0° C. After pouring into saturated $NaHCO_3$, phases were separated and the organic layer was dried over $MgSO_4$, filtered, concentrated, and purified by chromatography on silica gel (1/1, hexanes/EtOAc) to afford 1.1 g of 27 as a clear, colorless oil. ^{1}H NMR ($CDCl_3$) δ 8.04 (dd, J=7.0, 1.6, 1 H), 7.44 (m, 2 H), 7.12 (m, 1 H), 4.95 (dt, 1 H), 4.8 (m, 1 H), 4.7 (m, 2 H), 4.15–3.80 (m, 4 H), 3.5 (m, 2 H), 2.82 (dd, J=10.8,1 H), 2.55 (m, 2 H), 2.3 (m, 1 H), 2.1–1.3 (m, 6 H).

C: (5Z)-(9S, 11R, 15R)-11,15-Bis(tetrahydropyran-2-yloxy)-9-hydroxy-17,18,19,20-tetranor-16-(3-trifluoromethylphenoxy)-5-prostenoic Acid Isopropyl Ester (31)

To a solution of 2.1 g (3.9 mmol) of 27 in 100 mL of THF at −78° C. was added 3.9 mL (5.8 mmol) of a 1.5M solution of diisobutyaluminum hydride in toluene. The solution was stirred for 2 h, then quenched by the sequential addition of 0.4 mL of isopropanol at −78° C. followed by 0.4 mL of water at 23° C. Volatiles were removed under reduced pressure and the aqueous solution was extracted with Et_2O/EtOAc (1/1). Organic extracts were dried over $MgSO_4$, filtered, and concentrated to furnish 1.9 g of lactol 28.

To a 250 mL 3-necked round bottom flask equipped with a mechanical stirrer and a thermometer were added anhydrous DMSO (100 mL) and NaH (80% dispersion in mineral oil; 0.48 g, 16 mmol). The mixture was heated to 75° C. (internal) for 30 min, after which it was allowed to cool to room temperature for 1 h. Phosphonium bromide 29 (3.5 g,

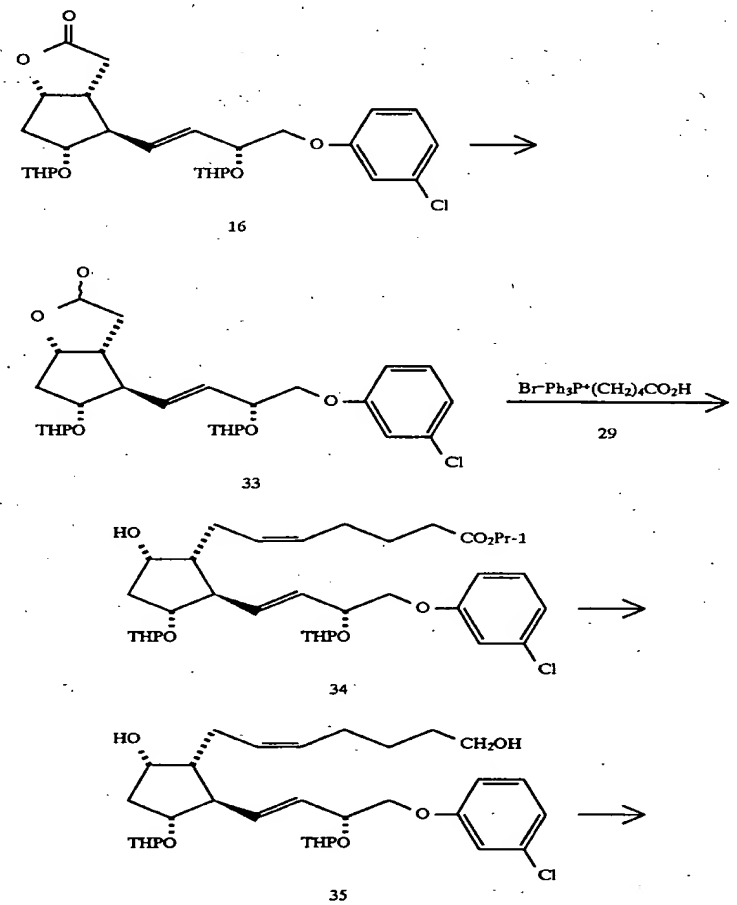
8 mmol) was then added. After stirring for 30 minutes, 1.9 g (3.5 mmol) of lactol 28 in 50 mL of DMSO was added, and the resulting solution was heated to 50° C. for 2 h and then brought to room temperature for 16 h. The solution was poured into 100 mL of water and approximately 2 mL of 50% NaOH added. The aqueous phase was extracted with ether (3×100 mL), then made acidic (pH=5.5) by the addition of a 10% citric acid solution, and extracted with EtO/hexanes, 2/1 (3×100 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to afford 1.9 g of 30 as a colorless oil.

To 1.9 g of carboxylic acid 30 dissolved in 10 mL acetone was added 0.95 g (6.0 mmol) of DBU and 1.0 g (6.1 mmol) of isopropyl iodide at 23° C. After 16 h, the solution was poured into 100 mL of water and extracted with 100 mL of EtOAc. The organic extract was dried over $MgSO_4$, filtered, concentrated, and purified by silica gel chromatography (3/2, hexanes/EtOAc) to afford 1.9 g of isopropyl ester 31 as a colorless oil. ^1H NMR ($CDCl_3$) δ 7.44 (t, 1 H), 7.12 (d, 1 H), 7.12 (dd, 2 H), 5.5–5.3 (m, 2 H), 4.99 (heptet, 1 H), 4.15–3.80 (m, 4 H), 2.82 (dd, J=10.8, 1 H), 2.55 (m, 2 H), 2.3 (m, 1 H), 2.1–1.3 (m, 24 H), 1.23 (s, 3 H), 1.20 (s, 3 H).

D: (5Z)-(9S, 11R, 15R)-17,18,19,20-Tetranor-16-(3-trifluoromethylphenoxy)-9,11,15-trihydroxy-5-prostenoic Acid Isopropyl Ester (6)

Ester 31 (1.9 g, 2.8 mmol) was dissolved in 14 mL of a mixture of AcOH/THF/H_2O (4/2/1) and the solution was heated to 50° C. for 1 h, allowed to cool to 23° C., poured into a saturated solution of $NaHCO_3$, and extracted with Et_2O (2×100 mL) and EtOAc (100 mL). The combined organic extracts were dried over $MgSO_4$, filtered, concentrated, and purified by silica gel chromatography (1/1, hexanes/EtOAc) to furnish 0.5 g of triol 6 as a clear, colorless oil. ^1H NMR ($CDCl_3$) δ 7.44 (t, J=7.8,1 H), 7.12 (dd, J=7.8, 2.0, 1 H), 7.12 (ddd, J=15.6, 7.2, 2.0, 2 H), 5.5–5.3 (m, 2 H), 4.99 (heptet, J=6.3, 1 H), 4.15–3.80 (m, 4 H), 3.2 (d, 1 H), 2.95 (s, 1 H), 2.82 (dd, J=10.8, 1 H), 2.75 (d, J=5.9, 1 H), 2.55 (m, 2 H), 2.3 (m, 1 H), 2.1–1.3 (m, 24 H), 1.23 (s, 3 H), 1.20 (s, 3 H). ^{13}C NMR ($CDCl_3$) δ 173.5, 158.7, 132.1, 131.5,130.0, 129.5, 129.2, 123.3, 120.8, 117.7, 117.6, 111.4, 111.4, 78.6, 74.4, 72.4, 69.9, 67.6, 52.6, 51.7, 42.5, 34.0, 31.5, 29.4, 26.8, 26.6, 24.9, 21.7.

EXAMPLE 3: Synthesis of Cloprostenol-1-ol (7)



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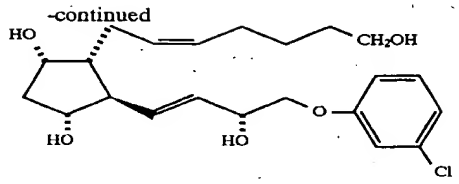


7

A: (5Z, 13E)-(9S, 11R, 15R)-11,15-Bis(tetrahydropyran-2-yloxy)-16-(3chlorophenoxy)-9-hydroxy-17,18,19,20-tetranor-5,13-prostadienoic Acid Isopropyl Ester (34)

A 1.5M solution of diisobutylaluminum hydride in toluene (10 mL, 15 mmol) was added dropwise to a solution of 5.8 g (11.4 mmol) of lactone 16 in 55 mL of THF at −78° C. After 1 h, 10 mL of methanol was added dropwise, and the mixture was stirred for 10 min at −78° C. before being warmed to room temperature. The mixture was then poured into 100 mL of a 1/1 solution of saturated aqueous potassium sodium tartrate/ethyl acetate and stirred. After separating layers, the aqueous phase was extracted with ethyl acetate (2×40 mL). Combined organic layers were dried over $MgSO_4$, filtered, concentrated, and purified by silica gel chromatography (3/2, ethyl acetate/hexane), to afford 4.4 g (76%) of lactol 33, which was used immediately in the next step.

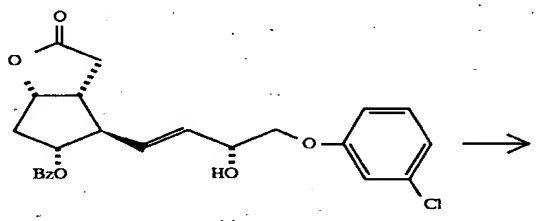
A 1M solution of potassium t-butoxide in THF (50.0 ml) was added dropwise to 12.1 g (27.3 mmol) of phosphonium salt 29 in 100 mL of THF at 0° C. After 30 min, a solution of 4.4 g (8.6 mmol) of lactol 33 in 20 mL of THF was added dropwise, and the mixture was stirred at room temperature overnight. The solution was then poured into 150 mL of a 1/1 mixture of ethyl acetate/saturated NH_4Cl. Layers were separated and the aqueous layer was extracted with ethyl acetate (2×100 mL). Combined organic layers were dried over $MgSO_4$, filtered, concentrated, and the residue was redissolved in 80 mL of acetone. To this was added 6.5 g (45 mmol) of DBU followed by 7.3 g (43 mmol) of isopropyl iodide. After stirring overnight, the reaction was poured into 100 mL of a 1/1 mixture of ethyl acetate/saturated NH_4Cl. Layers were then separated and the aqueous phase was further extracted with ethyl acetate (2×100 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated, and purified by silica gel chromatography (40% ethyl acetate in hexane) to afford 2.92 g (53% from lactone 16) of ester 34.

B: (5Z, 13E)-(9S, 11R, 15R)-16-(3-Chlorophenoxy)-17, 18,19,20-tetranor-9,11,15-trihydroxy-5,13-prostadienol (7)

A solution of 500 mg (0.79 mmol) of 34 in 10 mL of THF was added dropwise to 61 mg (1.60 mmol) of lithium aluminum hydride in 20 mL of THF at 0° C. After 40 min, the reaction was carefully poured into 15 mL of saturated NH_4Cl, and the mixture was then extracted with ethyl acetate (3×40 mL). Combined organic layers were dried over MgSO4 , filtered, and concentrated to afford 500 mg of crude 35.

To a solution of 500 mg of 35 in 20 mL of methanol was added 0.5 mL of 2M HCl. After 1 h, the reaction was quenched with 20 mL of saturated $NaHCO_3$ and the mixture was extracted with ethyl acetate (4×30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Silica gel s chromatography (EtOAc) provided 101 mg (31% from 34) of 7. ^{13}C NMR ($CDCl_3$) δ 159.27 (C), 135.44 (CH), 134.82 (C), 130.64 (CH), 130.26 (CH), 128.23 (CH), 121.25 (CH), 115.07 (CH), 113.08 (CH), 77.35 (CH), 72.35 (CH), 71.90 (CH_2), 70.89 (CH), 62.22 (CH_2), 55.40 (CH), 49.87 (CH), 42.79 (CH_2), 31.83 (CH_2), 26.77 (CH_2), 25.60 (CH_2), 25.33 (CH_2). Cl MS m/z calcd for $C_{22}H_{32}O_5Cl_1$ (MH^+) 411.1938, found 411.1938.

EXAMPLE 4: Synthesis of 13,14-Dihydrocloprostenol-1-ol Pivaloate (8)



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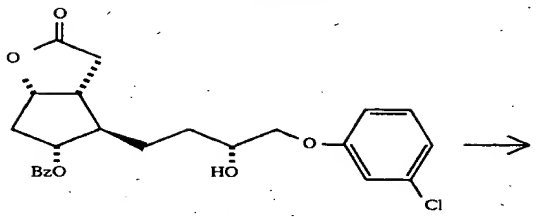

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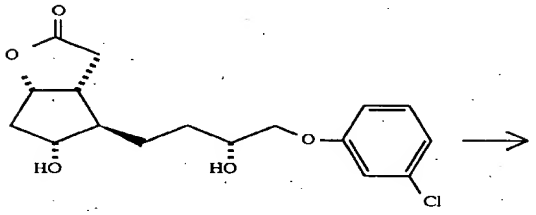

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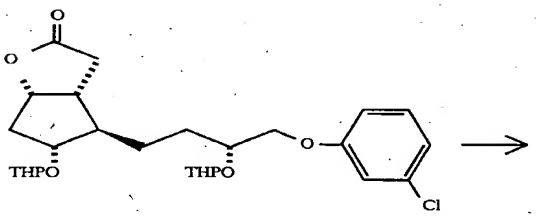

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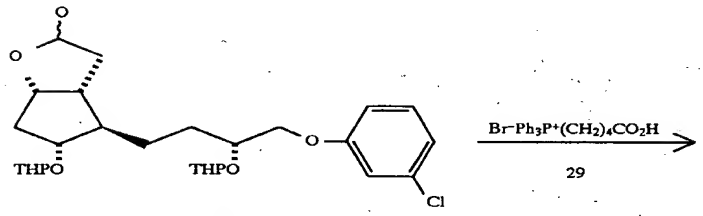

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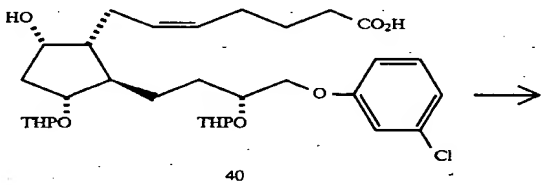

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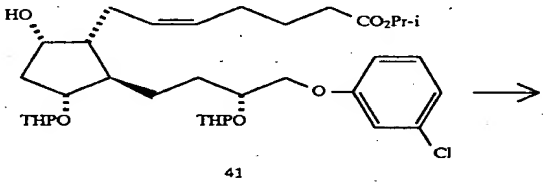

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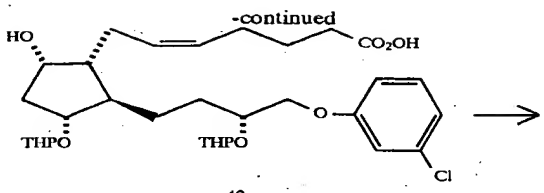

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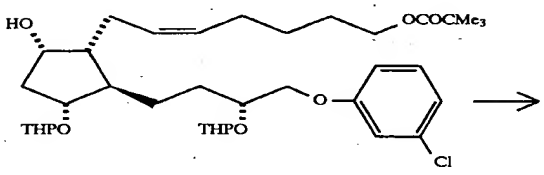

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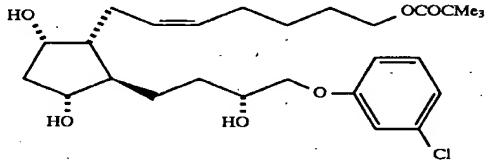


8

A: (3aR, 4R, 5R, 6aS)-4-[(3R)-4-(3-Chlorophenoxy)-3-hydroxybutyl]-5-hydroxy-hexahydro-2H-cyclopenta[b] furan-2-one (37):

A mixture of 2.4 g (5.4 mmol) of 14 and 250 mg of 10% (wt/wt) Pd/C in 35 mL of ethyl acetate was hydrogenated at 40 psi for 1 h. After filtration through a short pad of Celite®, the filtrate was evaporated down to 2.3 g (100%) of hydrogenated product 36.

The crude benzoate 36 was dissolved in 25 mL of methanol, and 610 mg (4.4 mmol) of K_2CO_3 was added. After 3.5 h, the mixture was poured into 100 mL of water/ethyl acetate (1/1). Layers were separated, and the aqueous phase was further extracted with ethyl acetate (2×50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Silica gel chromatography (EtoAc) provided 1.50 g (82%) of 37 as a white solid, m.p.=102.0°–103.5° C. ^1H NMR δ 7.22 (t, J=8.2 Hz, 1 H), 7.0–6.94 (m, 1 H), 6.91–6.88 (t, J=2.1 Hz, 1 H), 6.83–6.77 (m, 1 H), 4.97 (dt, J=3.0, 8.3 Hz, 1 H), 4.12–3.91 (m, 3 H), 3.82 (dd, J=7.4, 9.0 Hz, 1 H), 2.85 (dd, J=8.0, 16.5 Hz, 1 H), 2.6–1.4 (m, 11 H).

B: (3aR, 4R, 5R, 6aS)-4-[(3R)-4-(3-Chlorophenoxy)-3-(tetrahydropyran-2-yloxy)bulyl]-5-(tetrahydropyran-2-yloxy)-hexahydro-2H-cyclogenta[b]furan-2-one (38)

Diol 37 (3.4 g, 10 mmol) and 2.2 g (26 mmol) of 3,4-dihydro-2H-pyran were dissolved in 80 mL of CH_2Cl_2, and 240 mg (1.3 mmol) of p-toluenesulfonic acid monohydrate was added at 0° C. After 1 h, the reaction was poured into 50 mL of saturated $NaHCO_3$ and the mixture was extracted with CH_2Cl_2 (3×40 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated, and the residue was chromatographed on silica gel (hexane/ethyl acetate, 1/1) to afford 4.5 g (87%) of bis-THP ether 38.

C: (5Z)-(9S, 11R, 15R)-11,15-Bis(tetrahydropyran-2-yloxy)-16-(3-chlorophenoxy)-9-hydroxy-17,18,19,20-tetranor-5-prostenoic Acid IsoproDVl Ester (41)

A 1.5M solution of diisobutylaluminum hydride in toluene (1.8 mL, 2.7 mmol) was added to the solution 1.05 g (2.06 mmol) of 38 in 10 mL of THF at −78° C. After 1 h, 4 mL of methanol was added and the mixture was warmed to 25° C., then poured into 40 mL of ethyl acetate/saturated aqueous potassium sodium tartrate (1/1). Layers were separated and the aqueous phase was further extracted with ethyl acetate (3×30 mL). The combined organic layers were then dried over $MgSO_4$, filtered, concentrated, and the residue was chromatographed on silica gel (ethyl acetate) to afford 740 mg (70%) of lactol 39.

A 1.5M solution of potassium t-butoxide in THF (8.6 mL, 8.6 mmol) was added dropwise to a mixture of 15 mL of THF and 1.92 g (4.33 mmol) of phosphonium salt 29 at 0° C. After stirring for 1 h, a solution of 740 mg (1.45 mmol) of lactol 39 in 5 mL of THF was added dropwise, and the reaction was allowed to warm to 25° C. overnight. The mixture was then poured into 100 mL of ethyl acetate/saturated NH_4Cl (1/1). Layers were separated, and the aqueous phase was further extracted with ethyl acetate (2×70 mL). Combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford 1.6 g of crude acid 40.

Crude acid 40 (1.6 g) was dissolved in 11 mL of acetone and cooled to 0° C., then 850 mg (5.6 mmol) of DBU was added dropwise to the solution. The resulting mixture was stirred for 15 min at 0° C. and 30 min at 25° C., after which 850 mg (5.0 mmol) of isopropyl iodide was added. The reaction was stirred overnight and poured into 100 mL of ethyl acetate/saturated NH_4Cl (1/1). Layers were separated, and the aqueous phase was further extracted with ethyl acetate (2×50 mL). Combined organic layers were dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by silica gel chromatography (ethyl acetate/hexanes, 3/2) to afford 560 mg (61 % from lactol 39) of isopropyl ester 41.

D: (5Z)-(9S, 11R, 15R)-16-(3-Chlorophenoxy)-17,18,19,20-tetranor-9,11,15-trihydroxy-5-prostenol Pivaloate (8)

A solution of 400 mg (0.63 mmol) of 41 in 5 mL of THF was added dropwise to a suspension of 35 mg (0.92 mmol)

of lithium aluminum hydride in 5 mL of THF at 0° C. After 2 h, the reaction was poured into 50 mL of a 1/1 mixture of ethyl acetate/saturated $NaHCO_3$. The layers were then separated, and the aqueous phase was extracted with ethyl acetate (2×2 mL). Combined organic layers were dried over $MgSO_{41}$ filtered, and concentrated. The resulting residue was purified by silica gel chromatography (ethyl acetate) to afford 350 mg (95%) of diol 42.

Pivaloyl chloride (90 mg, 0.75 mmol) was added to a mixture of 350 mg (0.60 mmol) of 42, 60 mg (0.76 mmol) of pyridine, 22 mg (0.18 mmol) of 4(dimethylamino) pyridine, and 7 mL of CH_2Cl_2. After 1.5 h, the mixture was poured into 30 mL of saturated NH_4Cl/ethyl acetate (1/1). Layers were then separated and the aqueous phase was extracted with ethyl acetate (2×20 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated, and purified by silica gel chromatography (ethyl acetate/hexane, 3/2) to afford 370 mg (93%) of pivaloate 43.

Water (approximately 10 drops) and concentrated HCl (approximately 3 drops) were added to a solution of 370 mg (0.56 mmol) of 43 in 5 mL of methanol. After stirring overnight, the reaction was quenched by the addition of 20 mL of saturated $NaHCO_3$, and the mixture was extracted with ethyl acetate (3×20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed on silica gel (ethyl acetate/hexane, 3/2), to afford 165 mg (59%) of triol 8. ^{13}C NMR ($CDCl_3$) δ 178.77 (C), 159.27 (C), 134.80 (C), 130.20 (CH), 128.62 (CH), 121.19 (CH), 114.97 (CH), 112.97 (CH), 78.50 (CH), 74.46 (CH), 72.31 (CH_2), 69.86 (CH), 64.16 (CH_2), 52.53 (CH), 51.67 (CH), 42.50 (CH_2), 31.51 (CH_2), 29.40 (OH_2), 28.10 (OH_2), 27.12 (OH_3), 26.77 (CH_2), 26.65 (CH_2), 25.77 (CH_2). Cl MS, m/z calcd for $C_{27}H_{41}O_6Cl_1$ (MH^+), 497.2670, found 497.2656

EXAMPLE 5

$PGF_{2\alpha}$analogues are known to contract the iris sphincter of cats and this assay is a generally accepted reference for activity. For this reason, the pupil diameter of cats may be used to define the activity of $PGF_{2\alpha}$analogues and, as demonstrated by Stjernschantz and Resul (*Drugs Future,* 17:691–704 (1992)), predict the IOP-lowering potency.

Compounds of the present invention were therefore screened for pupillary constriction in the cat. Data for compounds 6, 7, and 8 are presented in Table 2, below. The response is quantitated as $Area_{1-5}$ values (area under the pupil diameter versus time curve from 1–5 hours), and the equivalent response dose (ED_5) is estimated from its dose response relationship.

TABLE 2

Cat Pupil Diameter Response

Compound	ED_5 (μg)
$PGF_{2\alpha}$ Isopropyl Ester	0.02
Cloprostenol Isopropyl Ester	0.01
6	0.2
7	0.02
8	0.06

Discussion:

The two standard compounds, $PGF_{2\alpha}$isopropyl ester and cloprostenol isopropyl ester, produced marked change in cat pupillary diameter, displaying ED_5 values of 0.02 and 0.01 jig, respectively. Compound 7 (cloprostenol-1-ol) and compound 8 (13,14-dihydrocloprostenol-1-ol pivaloate), displayed nearly equivalent potency. 13,14-Dihydrofluprostenol isopropyl ester (compound 6) was approximately one order of magnitude less potent, with an ED_5 of 0.2 μg.

EXAMPLE 6

In the study presented below, compound 6 (Table 1, above) was tested for IOP-lowering effect in cynomolgus monkey eyes.

The right eyes of the cynomolgus monkeys used in this study were previously given laser trabeculoplasty to induce ocular hypertension in the lasered eye. Animals had been trained to sit in restraint chairs and conditioned to accept experimental procedures without chemical restraint. IOP was determined with a pneumatonometer after light corneal anesthesia with dilute proparacaine. The test protocol included a five-dose treatment regimen because of the typical delayed response to prostaglandins. The designated test formulations were administered to the lasered right eyes, and the normal left eyes remained untreated, although IOP measurements were taken. Baseline IOP values were determined prior to treatment with the test formulation, and then IOP was determined from 1 to 7 hours after the first dose, 16 hours after the fourth dose, and 1 to 4 hours after the fifth dose.

The equivalent response dose (ED_{20}) is estimated from the dose response relationship to be the dose producing a 20% peak reduction in IOP.

TABLE 3

Monkey IOP Response

Compound	ED_{20} (μg)
$PGF_{2\alpha}$ Isopropyl Ester	0.4
6	0.3

Discussion:

As can be seen in Table 3, compound 6, the 13,14-dihydro analogue of fluprostenol was quite potent in the monkey IOP model, producing a 20% reduction at 0.3 μg. This was even more potent than the standard compound, $PGF_{2\alpha}$isopropyl ester.

EXAMPLE 7

The following Formulations 1–4 are representative pharmaceutical compositions of the invention for topical use in lowering of intraocular pressure. Each of Formulations 1 through 4 may be formulated in accordance with procedures known to those skilled in the art.

FORMULATION 1

Ingredient	Amount (wt %)
Compound 5 (Table 1)	0.002
Dextran 70	0.1
Hydroxypropyl methylcellulose	0.3
Sodium chloride	0.77
Potassium chloride	0.12
Disodium EDTA	0.05
Benzalkonium chloride	0.01
HCl and/or NaOH	pH 7.2–7.5
Purified water	q.s. to 100%

FORMULATION 2

Ingredient	Amount (wt %)
Compound 6 (Table 1)	0.01
Monobasic sodium phosphate	0.05
Dibasic sodium phosphate (anhydrous)	0.15
Sodium chloride	0.75
Disodium EDTA	0.01
Benzalkonium chloride	0.02
Polysorbate 80	0.15
HCl and/or NaOH	pH 7.3–7.4
Purified water	q.s.to 100%

FORMULATION 3

Ingredient	Amount (wt %)
Compound 7 (Table 1)	0.001
Dextran 70	0.1
Hydroxypropyl methylcellulose	0.5
Monobasic sodium phosphate	0.05
Dibasic sodium phosphate (anhydrous)	0.15
Sodium chloride	0.75
Disodium EDTA	0.05
Benzalkonium chloride	0.01
NaOH and/or HCl	pH 7.3–7.4
Purified water	q.s. to 100%

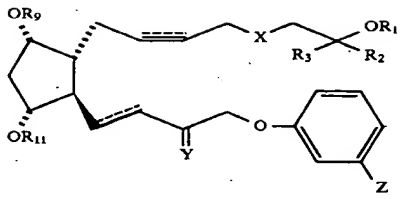
FORMULATION 4

Ingredient	Amount (wt %)
Compound 8 (Table 1)	0.003
Monobasic sodium phosphate	0.05
Dibasic sodium phosphate (anhydrous)	0.15
Sodium chloride	0.75
Disodium EDTA	0.05
Benzalkonium chloride	0.01
HCl and/or NaOH	pH 7.3–7.4
Purified water	q.s. to 100%

The invention has been described by reference to certain preferred embodiments; however, it should be understood that it may be embodied in other specific forms or variations thereof without departing from its spirit or essential characteristics. The embodiments described above are therefore considered to be illustrative in all respects and not restrictive, the scope of the invention being indicated by the appended claims rather than by the foregoing description.

What is claimed is:

1. A method of treating glaucoma and ocular hypertension which comprises topically administering to the affected eye a composition comprising a therapeutically effective amount of a compound having the absolute stereochemical structure of the following formula (IV), and being substantially free of the enantiomer of said compound:



(IV)

wherein:

R_1 =H; C_1–C_{12} straight-chain or branched alkyl; C_1–C_{12} straight-chain or branched acyl; C_3–C_3 cycloalkyl; or a cationic salt moiety;

R_2, R_3 =H, or C_1–C_5 straight-chain or branched alkyl; or R_2 and R_3 taken together may represent O;

X=O, S, or CH_2;

- - - represents any combination of a single bond, or a cis or trans double bond for the alpha (upper) chain; and a single bond or trans double bond for the omega (lower) chain;

R_9=H, C_1–C_{10} straight-chain or branched alkyl, or C_1–C_{10} straight-chain or branched acyl;

R_{11}=H, C_1–C_{10} straight-chain or branched alkyl, or C_1–C_{10} straight-chain or branched acyl;

Y=O; or H and OR_{15} in either configuration wherein R_{15}=H, C_1–C_{10} straightchain or branched alkyl, or C_1–C_{10} straight-chain or branched acyl; and

Z=Cl or CF_3;

with the proviso that when R_2 and R_3 taken together represent O, then R_1≠C_1–C_{12} straight-chain or branched acyl; and when R_2=R_3=H, then R_1 ≠a cationic salt moiety; and

with the further proviso that the following compound be excluded:

cyclopentane heptenol-5-cis-2-(3-αhydroxy-4-m-chlorophenoxy-1-transbutenyl)-3,5 dihydroxy, [1_α, 2_β, 3_α, 5_α].

2. The method of claim 1, wherein for the compound (IV):

R_2, R_3 taken together represent O;

X=CH_2;

- - - represents a cis double bond for the alpha (upper) chain and a trans double bond for the omega (lower) chain;

R_9 and R_{11}=H; and

Y=OH in the alpha configuration and H in the beta configuration.

3. The method of claim 2, wherein for the compound (IV): Z=CF_3.

4. The method of claim 1, wherein: R_2 =R_3=H, or R_2 and R_3 taken together represent O; X=O or CH_2; R_9=R_{11}=H; Y=H and OR_{15}; and R_{15}=H.

5. The method of claim 4, wherein: R_1=H, C_1–C_{12} straight chain or branched alkyl or cationic salt moiety; and R_2 and R_3 taken together represent O.

6. The method of claim 5, wherein the compound of formula (IV) is selected from the group consisting of 3-oxacloprostenol, 13,14-dihydrofluprostenol, and their pharmaceutically acceptable esters and salts.

7. The method of claim 4, wherein: R_1 =H or C_1–C_{12} straight chain or branched acyl; and R_2=R_3=H.

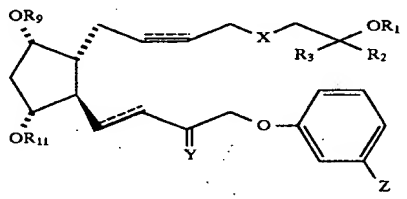
8. The method of claim 7, wherein the compound formula (IV) is 13,14dihydrocloprostenol pivaloate.

9. The method of claim 1, wherein between about 0.01 and about 1000 μg/eye of the compound is administered.

10. The method of claim 9, wherein between about 0.1 and about 100 μg/eye of the compound is administered.

11. The method of claim 10, wherein between about 0.1 and about 10 μg/eye of the compound is administered.

12. A topical ophthalmic composition for the treatment of glaucoma and ocular hypertension comprising an ophthalmically acceptable carrier and a therapeutically effective amount of a compound having the absolute stereochemical structure of the following formula (IV), and being substantially free of the enantiomer of said compound:



(IV)

wherein:

R_1=H; C_1–C_{12} straight-chain or branched alkyl; C_1–C_{12} straight-chain or branched acyl; C_3–C_8 cycloalkyl; or a cationic salt moiety;

R_2, R_3=H, or C_1–C_5 straight-chain or branched alkyl; or R_2 and R_3 taken together may represent O;

X=O, S, or CH_2;

⁻ ⁻ ⁻ represents any combination of a single bond, or a cis or trans double bond for the alpha (upper) chain; and a single bond or trans double bond for the omega (lower) chain;

R_9=H, C_1–C_{10} straight-chain or branched alkyl, or C_1–C_{10} straight-chain or branched acyl;

R_{11}=H, C_1–C_{10} straight-chain or branched alkyl, or C_1–C_{10} straight-chain or branched acyl;

Y=O; or H and OR_{15} in either configuration wherein R_{15}=H, C_1–C_{10} straight-chain or branched alkyl, or C_1–C_{10} straight-chain or branched acyl; and

Z=Cl or CF_3;

with the proviso that when R_2 and R_3 taken together represent O, then R_1≠C_1–C_{12} straight-chain or branched acyl; and when R_2 =R_3 =H, then R_1≠a cationic salt moiety; and

with the further proviso that the following compound be excluded:

cyclopentane heptenol-5-cis-2-(3-μhydroxy4-m-chlorophenoxy-l1-transbutenyl)-3,5 dihydroxy, [1_α, 2_β, 3_α, 5_α].

13. The composition of claim 12, wherein for the compound (IV):

R_2, R_3 taken together represent O;

X=CH_2;

⁻ ⁻ ⁻ represents a cis double bond for the alpha (upper) chain and a trans double bond for the omega (lower) chain;

R_9 and R_{11}=H; and

Y=OH in the alpha configuration and H in the beta configuration.

14. The composition of claim 13, wherein for the compound (IV): Z=CF_3.

15. The composition of claim 12, wherein: R_2=R_3=H, or R_2 and R_3 taken together represent O; X=O or CH_2; R_9=R_{11}=H; Y=H and OR_{15}; and R_{15}=H.

16. The composition of claim 15, wherein: R_1=H, C_1–C_{12} straight chain or branched alkyl, or cationic salt moiety; and R_2 and R_3 taken together represent O.

17. The composition of claim 16, wherein the compound of formula (IV) is selected from the group consisting of 3-oxacloprostenol, 13,14-dihydrofluprostenol, and their pharmaceutically acceptable esters and salts.

18. The composition of claim 15, wherein: R_1=H or C_1–C_{12} straight chain or branched acyl; and R_2=R_3=H.

19. The composition of claim 18, wherein the compound of formula (IV) is dihydrocloprostenol pivaloate.

20. The composition of claim 12, wherein the concentration of the compound of formula (IV) is between about 0.0003 and about 0.3 wt %.

21. The composition of claim 20, wherein the concentration of the compound of formula (IV) is between about 0.0003 and about 0.3 wt %.

22. The composition of claim 21, wherein the concentration of the compound of formula (IV) is between about 0.003 and about 0.03 wt %.

* * * * *

ATTACHMENT B

IN THE UNITED STATES PATENT OFFICE

Express Mail EL008174427US

In re Application of Klimko et al.

Serial No. 08/917,795

Filed: August 21, 1997

Examiner: R. Raymond

Group Art Unit: 1611

For: Use of Cloprostenol and Fluprostenol Analogues
To Treat Glaucoma and Ocular Hypertension

TERMINAL DISCLAIMER UNDER 37 C.F.R. §1.321(b) and (c)

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Alcon Laboratories, Inc. ("Alcon") is the owner of the entire interest in the above-identified patent application and related United States Patent Nos. 5,510,383 (issued April 23, 1996) and 5,665,773 (issued September 9, 1997), as demonstrated by the attached assignment documents and notices of recordation for application Serial No. 08/917,795. The present application, the '773 patent, and the '383 patent are derived from USSN 08/101,598 filed on August 3, 1993 (now abandoned).

Alcon hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application, which would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. 154 to 156 and 173, as presently shortened by any terminal disclaimer, of U.S. Patent No. 5,510,383 (referred to hereinafter as the prior patent). Alcon hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs

with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

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Respectfully submitted,

ALCON LABORATORIES, INC.

Date 9-15-18

By _____
Barry L. Copeland
Registration No. 34,801

ADDRESS FOR CORRESPONDENCE:
Barry L. Copeland [Mail Code Q-148]
Intellectual Property Law & R&D Counsel
ALCON LABORATORIES, INC.
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Attorney Docket No.: 1407B

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JULIE J. L. CHENG
PATENT DEPT., MC Q-148
ALCON LABORATORIES, INC.
6201 SOUTH FREEWAY
FORT WORTH, TX 76134-2099

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ASSIGNOR:
KLIMKO, PETER G. DOC DATE: 07/26/94

ASSIGNOR:
BISHOP, JOHN E. DOC DATE: 07/26/94

ASSIGNOR:
SALLEE, VERNEY L. DOC DATE: 07/26/94

RECORDATION DATE: 09/21/94 NUMBER OF PAGES 004 REEL/FRAME 7143/0817

DIGEST : ASSIGNMENT OF ASSIGNORS INTEREST

ASSIGNEE:
ALCON LABORATORIES, INC.
PATENT DEPARTMENT, MC Q-148
6201 SOUTH FREEWAY
FORT WORTH, TX 76134-2099

SERIAL NUMBER 8-280681 FILING DATE 07/26/94
PATENT NUMBER ISSUE DATE 00/00/00

EXAMINER/PARALEGAL
ASSIGNMENT BRANCH
ASSIGNMENT/CERTIFICATION SERVICES DIVISION

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1-31-92

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Peter G. Klimko
John E. Bishop
Verney L. Sallee

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3. Nature of conveyance:
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Execution Date: July 26, 1994

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Name: Alcon Laboratories, Inc.

Internal Address: Patent Department, MC Q-148

Street Address: 6201 South Freeway

City: Fort Worth State: TX ZIP: 76134-2099

Additional name(s) & address(es) attached? ☐ Yes ☒ No

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application is: _____

A. Patent Application No.(s)
08/280,681

B. Patent No.(s)

Additional numbers attached? ☐ Yes ☒ No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: Julie J. L. Cheng

Internal Address: Patent Dept., MC Q-148
ALCON LABORATORIES, INC.

Street Address: 6201 South Freeway

City: Fort Worth State: TX ZIP: 76134-2099

6. Total number of applications and patents involved: 1

7. Total fee (37 CFR 3.41).....$ 40.00

☐ Enclosed

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9. Statement and signature.
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Julie J. L. Cheng
Name of Person Signing

Signature

9/16/94
Date

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ASSIGNMENT

WHEREAS I am a below named inventor of the invention entitled:

"USE OF CLOPROSTENOL AND FLUPROSTENOL ANALOGUES TO TREAT GLAUCOMA AND OCULAR HYPERTENSION "

and described in a United States Patent Application filed with the United States Patent and Trademark Office on July 26, 1994, and further identified by Attorney Docket No. 1407.

WHEREAS, ALCON LABORATORIES, INC., a company organized under the laws of Delaware and having a place of business at 6201 South Freeway, Fort Worth, Texas, 76134, is desirous of acquiring the entire right, title and interest in and to said invention and to any and all Letters Patent of the United States and foreign countries which may be obtained therefor;

NOW, THEREFORE, for good and valuable consideration, I do hereby sell, assign and transfer to ALCON LABORATORIES, INC., its legal representatives, successors, and assigns, the entire right, title and interest in and to said invention as set forth in the above-mentioned application, and in and to any and all patents of the United States and foreign countries which may be issued for said invention;

UPON SAID CONSIDERATIONS, I hereby agree that I will not execute any writing or do any act whatsoever conflicting with these presents, and that I will, at any time upon request, without further or additional consideration but at the expense of said assignee, execute such additional assignments and other writings and do such additional acts as said assignee may deem necessary or desirable to perfect the assignee's enjoyment of this grant and render all necessary assistance in making application for and obtaining original, divisional, reexamined, reissued, or other Letters Patent of the United States or of any and all foreign countries on said invention and in enforcing any rights in action accruing as a result of such applications or patents, said assistance to include my cooperation in all

prosecution associated with obtaining such applications or patents and my provision of testimony in any proceedings or transactions involving such applications or patents, it being understood that the foregoing covenant and agreement shall bind, and inure to the benefit of, the assigns and legal representatives of assignor and assignee.

AND I request the Commissioner of Patents and Trademarks to issue any Letters Patent of the United States which may be issued for said invention to said ALCON LABORATORIES, INC., its legal representatives, successors or assigns, as the sole owner of the entire right, title and interest in said patent and the invention covered thereby.

Full name of inventor: Peter G. Klimko

Inventor's Signature: Peter G. Klimko

Date: 7/22/94

Residence/Post Office Address: 5301 Overton Ridge, #1206

Ft. Worth, Texas 76132

Citizenship: United States

STATE OF TEXAS §
§
COUNTY OF TARRANT §

On this 22nd day of July 1994, before me personally appeared Peter G. Klimko, to me known to be the person named in and who executed the above instrument, and acknowledged to me he executed the same for the uses and purposes therein set forth.

PHYLISS A. EWING
NOTARY PUBLIC
State of Texas
Comm. Exp. 10-03-96

Notary Public

Full name of inventor: John E. Bishop

Inventor's Signature: John E. Bishop

Date: 22 July 1994

Residence/Post Office Address: 18 Chadwick Circle, Apt. B

Nashua, New Hampshire 03062

Citizenship: United States

STATE OF TEXAS §
§
COUNTY OF TARRANT §

On this 22nd day of July 1994 before me personally appeared John E. Bishop, to me known to be the person named in and who executed the above instrument, and acknowledged to me he executed the same for the uses and purposes therein set forth.

PHYLISS A. EWING
NOTARY PUBLIC
State of Texas
Comm. Exp. 10-03-96

Phyliss A. Ewing
Notary Public

Full name of inventor: Verney L. Sallee

Inventor's Signature: Verney L. Sallee

Date: July 29, 1994

Residence/Post Office Address: 304 Diamond Lane

Burleson, Texas 76023

Citizenship: United States

STATE OF TEXAS §
§
COUNTY OF TARRANT §

On this 25th day of July 1994 before me personally appeared Verney L. Sallee, to me known to be the person named in and who executed the above instrument, and acknowledged to me he executed the same for the uses and purposes therein set forth.

PHYLISS A. EWING
NOTARY PUBLIC
State of Texas
Comm. Exp. 10-03-96

Phyliss A. Ewing
Notary Public

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JUNE 06, 1997

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ALCON LABORATORIES, INC.
BARRY L. COPELAND
PATENT DEPARTMENT (Q-148)
6201 SOUTH FREEWAY
FORT WORTH, TX 76134-2099

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RECORDATION DATE: 04/25/1997

REEL/FRAME: 8467/0681
NUMBER OF PAGES: 3

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:
ZINKE, PAUL W.

DOC DATE: 04/21/1997

ASSIGNEE:
ALCON LABORATORIES, INC.
6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134

SERIAL NUMBER: 08769293
PATENT NUMBER:

FILING DATE: 12/18/1996
ISSUE DATE:

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☐ Security Agreement ☐ Change of Name

☐ Other _____

Execution Date: April 21, 1997

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Name: Alcon Laboratories, Inc.,

Address: 6201 South Freeway
Fort Worth, Texas 76134

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4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application is: _____

A. Patent Application No.(s)

08/769,293

B. Patent No.(s)

Additional numbers attached? ☐ Yes X No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: Barry L. Copeland

Internal Address: Patent Department (Q-148)

ALCON LABORATORIES, INC.

Street Address: 6201 South Freeway

City: Fort Worth State: TX ZIP: 76134-2099

6. Total number of applications and patents involved:
one (1)

7. Total fee (37 CFR 3.41).....$ 40.00

☐ Enclosed

X Authorized to be charged to deposit account

8. Deposit account number:

01-0682

(Attach duplicate copy of this page if paying by deposit account)

DO NOT USE THIS SPACE

9. Statement and signature.
To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Barry L. Copeland Reg. No. 34,801
Name of Person Signing

Signature

4-24-97
Date

Docket 1560

Total number of pages including cover sheet 3

CMB No. 0651-0011 (exp. 4/94)

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Washington, D.C. 20231

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MRD 04-25-97

ASSIGNMENT

WHEREAS I am a below named inventor of the invention entitled:

USE OF CLOPROSTENOL AND FLUPROSTENOL ANALOGUES TO TREAT GLAUCOMA AND OCULAR HYPERTENSION

and described in a United States Patent Application filed with the United States Patent and Trademark Office on December 18, 1996, Serial No. 08/769,293 and further identified by Attorney Docket No. 1407A; and

WHEREAS, ALCON LABORATORIES, INC., a company organized under the laws of Delaware and having a place of business at 6201 South Freeway, Fort Worth, Texas, 76134, is desirous of acquiring the entire right, title and interest in and to said invention and to any and all Letters Patent of the United States and foreign countries which may be obtained therefor;

NOW, THEREFORE, for good and valuable consideration, I do hereby sell, assign and transfer to ALCON LABORATORIES, INC., its legal representatives, successors, and assigns, the entire right, title and interest in and to said invention as set forth in the above-mentioned application, and in and to any and all patents of the United States and foreign countries which may be issued for said invention;

UPON SAID CONSIDERATIONS, I hereby agree that I will not execute any writing or do any act whatsoever conflicting with these presents, and that I will, at any time upon request, without further or additional consideration but at the expense of said assignee, execute such additional assignments and other writings and do such additional acts as said assignee may deem necessary or desirable to perfect the assignee's enjoyment of this grant and render all necessary assistance in making application for and obtaining original, divisional, continuation-in-part, reexamined,

reissued, or other Letters Patent of the United States or of any and all foreign countries on said invention and in enforcing any rights in action accruing as a result of such applications or patents, said assistance to include my cooperation in all prosecution associated with obtaining such applications or patents and my provision of testimony in any proceedings or transactions involving such applications or patents, it being understood that the foregoing covenant and agreement shall bind, and inure to the benefit of, the assigns and legal representatives of assignor and assignee.

AND I request the Commissioner of Patents and Trademarks to issue any Letters Patent of the United States which may be issued for said invention to said ALCON LABORATORIES, INC., its legal representatives, successors or assigns, as the sole owner of the entire right, title and interest in said patent and the invention covered thereby.

Full name of inventor:	**PAUL W. ZINKE**
Inventor's signature:	Paul W. Zinke
Date:	April 21, 1997
Residence and Post Office Address:	4129 Willow Way Road Fort Worth, Texas 76133
Citizenship:	United States

STATE OF TEXAS §
§
COUNTY OF TARRANT §

On this 21 day of April, 1997, before me personally appeared **PAUL W. ZINKE**, to me known to be the person named in and who executed the above instrument, and acknowledged to me he/she executed the same for the uses and purposes therein set forth.

Dawn Fedyniak
Notary Public

DAWN FEDYNIAK
MY COMMISSION EXPIRES
September 22, 1997

Atty Docket 1407A

ATTACHMENT C

IND 51,000

AL-6221 SOLUTION
TRAVAPROST

Date Submitted: June 28, 1996

Date Approved: July 28, 1996

AMENDMENTS
VOLUME 1

1	Jul 08, 1996	ACKNOWLEDGEMENT OF RECEIPT ON 6/28/96. 51,000 ASSIGNED.
2	Jul 17, 1996	001: EXPLANATION OF DATA UNDER HEADING "% CHANGE FROM BASELINE".
3	Aug 15, 1996	001: AMENDMENT TO C-96-52; CHANGE IN ENTRANCE CRITERIA; CHANGE IN TESTING SCHEDULE & ADDITIONAL SAFETY PARAMETERS.
4	Oct 15, 1996	002: NEW HPLC ASSAY; REVISION IN SPECIFICATION FOR NEWLY IDENTIFIED IMPURITIES.
5	Mar 21, 1997	003: NEW PROTOCOL C-97-02 SAFETY STUDY; CAINE, EVANS, LAIBOVITZ, MORRIS, MUNDORF, WALTERS AND WILLIAMS INVESTIGATORS.
6	Apr 08, 1997	004: CHANGE TO POLYOXYL 40 CASTOR OIL; PP CLOSURES.
7	May 02, 1997	005: ADD R.H. STEWART AS INVESTIGATOR FOR C-97-02.
8	Jun 17, 1997	006: REQUEST FOR END OF PHASE 2 MEETING.
9	Aug 21, 1997	007: ANNUAL REPORT

CONTINUED IN VOLUME 2

IND 51,000

AL-6221 SOLUTION
TRAVAPROST

Date Submitted: June 28, 1996

Date Approved: July 28, 1996

AMENDMENTS
VOLUME 2

1	Sep 11, 1997	008: TR119:38520:0896 REQUESTED IN FULL (SUMMARIZED IN ANNUAL REPORT). 2 OTHER TR'S REQUESTED ARE NOT COMPLETE.
2	Sep 16, 1997	009: END OF PHASE II BRIEFING PACKET & PRE-IND BRIEFING PACKET FOR HPB.

CONTINUED IN VOLUME 3

IND 51,000

AL-6221 SOLUTION
TRAVAPROST

Date Submitted: June 28, 1996

Date Approved: July 28, 1996

AMENDMENTS
VOLUME 3

1	Dec 18, 1997	SN:010	PROTOCOL C-97-71 FOR PHASE III STUDY. INVESTIGATORS: BEEHLER, CAINE, MANDELL, ROTBERG, SCHENKER, STEVENSON, STEWART, WASSERSTROM, WILLIAMS, SALL.

CONTINUED IN AMENDMENTS VOLUME 4

IND 51,000

AL-6221 SOLUTION
TRAVAPROST

Date Submitted: June 28, 1996

Date Approved: July 28, 1996

AMENDMENTS
VOLUME 4

1	Jan 14, 1998	SN011: ADDITION OF 14 INVESTIGATORS TO C-97-71. CALDWELL, CAMPBELL, CAMRAS, DEHNING, EVANS, HENRY, MORRISON, MUNDORF, ORENGO-NANIA, SALL, SHARPE, SHIN, STEWART & STILES.

CONTINUED IN AMENDMENTS VOLUME #5

IND 51,000

AL-6221 SOLUTION
TRAVAPROST

Date Submitted: June 28, 1996

Date Approved: July 28, 1996

AMENDMENTS
VOLUME 5

1	Feb 04, 1998	SN012: ADDITION OF 8 INVESTIGATORS TO C-97-71. R.LEWIS, P.NETLAND, G.THORNE, D.DAY, P.SIDOTI, R:STURM, W.MARCH & M.WEISS.
2	Feb 18, 1998	SN:013 NEW SAFETY & EFFICACY STUDY C-97-72. INVESTIGATORS BROTHERMAN, DIETLEIN, FRIEDMAN, LAIBOVITZ, MCMENEMY, SIMMONS & WALTERS.
3	Feb 19, 1998	SN:014 NEW INVESTIGATORS TO C-97-71 - ASSIL, CHURNER & DUBINER.
4	Feb 27, 1998	SN:015 - NEW PROTOCOL C-97-73 & NEW INVESTIGATORS: BEARMAN, CHOPRA, COX, LUO, SALL & WALTERS. NEW INVESTIGATORS TO C-97-72: CATHERINE BIRT, NEERU GUPTA.
5	Feb 27, 1998	SN:016 - IND SAFETY REPORT - FINDINGS OF TERATOGENICITY.
6	Mar 03, 1998	SN:017 NEW INVESTIGATORS TO C-97-73....H.DOYLE, D.HALL, M.PORIAS, J.ROBERTS, J.WHITSETT.

CONTINUED IN AMENDMENTS VOLUME 6

IND 51,000

AL-6221 SOLUTION
TRAVAPROST

Date Submitted: June 28, 1996

Date Approved: July 28, 1996

AMENDMENTS
VOLUME 6

1	Mar 06, 1998	SN:018 IND AMENDMENT A)INFO SUPPORTING CHIROSCIENCE AS MFG; B) REVISED SPECS/UPDATED TEST METHODS FOR DRUG SUBSTANCE; C) Q/Q FORMULAE; D) REVISED & UPDATED TESTS & SPECS BEING APPLIED TO CLIN.STUDIES; E) ID OF PKG MATERIALS BEING USED IN PHASE III PROGRAM.
2	Mar 09, 1998	SN:019 UPDATED CLINICAL INVESTIGATOR'S BROCHURE.

CONTINUED IN AMENDMENTS VOLUME 7

IND 51,000

AL-6221 SOLUTION
TRAVAPROST

Date Submitted: June 28, 1996

Date Approved: July 28, 1996

AMENDMENTS
VOLUME 7

1	Mar 18, 1998	SN:020 ADDING INVESTIGATORS: C9771: GALIN, MARES, SILVERSTONE, SMITH. C9772: CACIOPPO, GREENIDGE, LAMPING, MCCURDY, MCMAHON, REINSTEIN, ROBIN, SHIELDS, THATCHER, WHITSON. C9773: ATLAS, CHARLTON, CRAVEN, HELMS, HURVITZ, KAUFMAN, KRUG, LEVY, MITCHELL, NELSON, PATCHETT, ROTHBERG, STEWART, STURM, TAUBER.
2	Apr 08, 1998	SN:021 ADD INVESTIGATORS TO C-97-72: COHEN, JOOS, TERRY, KATZMAN, LOPATYNSKY, PILCHARD AND SERLE.
3	Apr 10, 1998	SN:022 ADDING INVESTIGATOR TO C-97-73: R.A. LAIBOVITZ.
4	Apr 22, 1998	SN:023 PROTOCOL C-97-71 ADDING INVESTIGATORS: J. BOKOSKY, R. STAMPER, M. KOTTLER, M. WEITZMAN, AND J. SPADAFORA.
5	Apr 22, 1998	SN:024 C-97-72 ADDING CROS': GAYNELL PILCHER, BEVERLY MILLER, LINDA SINCLAIR, VICKI RANDOLPH, & SUHAIL SAFFO.

CONTINUED IN AMENDMENTS VOLUME 8

IND 51,000

AL-6221 SOLUTION
TRAVAPROST

Date Submitted: June 28, 1996

Date Approved: July 28, 1996

AMENDMENTS
VOLUME 8

1	May 12, 1998	SN:025 PROTOCOL C-97-72 NEW INVESTIGATORS -- LEHRER, PICKETT, RICE AND ROSANELLI.
2	May 12, 1998	SN:026 C-97-72 ADDING KARIM F.DAMJI AS INVESTIGATOR IN CANADA.
3	May 18, 1998	SN:027 C-97-73 - ADDING DAVID P.TINGEY AS INVESTIGATOR IN CANADA.
4	May 28, 1998	SN:028 AMENDMENT TO C-97-73 RESTRICTS LOWER AGE IN INCLUSION CRITERIA TO AGE 18 [APPLIES TO CANADIAN INVESTIGATORS ONLY].
5	Jun 10, 1998	SN:029 2 AMENDMENTS TO C-97-72. ONE RESTRICTS LOWER AGE IN INCLUSION CRITERIA TO 18 FOR CANADIAN INVESTIGATORS ONLY, AND THE SECOND ADDS DEAN CARLSON, RONALD FELLMAN, AND PAUL MICHELSON TO US STUDY.
6	Jun 15, 1998	SN:030 C-97-73 ADDING INVESTIGATORS, B.FRANCIS, R.FELLMAN, E.G.ROSANELLI, D.STEVENSON, G.THORNE, & B.WESTON.
7	Jul 14, 1998	SN:031 ADD R.M.FELDMAN & W.W.MCMULLEN AS INVESTIGATORS TO PROTOCOL C-97-73.
8	Jul 28, 1998	SN:032 ADD TODD SEVERIN AS INVESTIGATOR TO C-97-71. ADD M.BURKE, M.BERNSTEIN, T.CROLEY & J.BACHARACH TO C-97-72.
9	Aug 04, 1998	SN:033 : ADD R.FELDMAN AS INVESTIGATOR TO C-97-71.

CONTINUED IN AMENDMENTS VOLUME 9

IND 51,000

AL-6221 SOLUTION
TRAVAPROST

Date Submitted: June 28, 1996

Date Approved: July 28, 1996

AMENDMENTS
VOLUME 9

1	Aug 07, 1998	SN:034 NEW PROTOCOL C-97-77 AND INVESTIGATORS: BIRT, CARLSON, DAMJI, DIETLEIN, GREENIDGE, GUPTA, JOOS, LAMPING, LEHRER, MCCURDY, MCMAHON, SIMMONS, BROTHERMAN, BURKE, CACIOPPO, CROLEY, FELLMAN, FRIEDMAN, KATZMAN, LOPATYNSKI, MICHELSON, PICKETT, RICE, ROBIN, ROSANELLI, TERRY, BACHARACH BERNSTEIN, MONTGOMERY, PILCHARD, REINSTEIN, SHIELDS, THATCHER, WALTERS, WHITSON. (35).

CONTINUED IN AMENDMENTS VOLUME 10

IND 51,000

AL-6221 SOLUTION
TRAVAPROST

Date Submitted: June 28, 1996

Date Approved: July 28, 1996

AMENDMENTS
VOLUME 10

1	Aug 11, 1998	SN:035 C-97-73 ADD NEW INVESTIGATORS: DONALD BROTHERMAN, ROBERT CAINE, DOUGLAS DAY, RAYMOND HERNANDEZ, JEFFREY WASSERSTROM AND MARK WEISS.
2	Sep 04, 1998	SN:036 C-97-77 ADDING NEW INVESTIGATORS:ATLAS, BEARMAN, BOKOWSKY, CAIN, CALDWELL, CAMRAS, CANTOR, CHURNER, CHOPRA, COS, CRAVEN, DAY, DUBINER, DEHNING, DOYLE, EVANS, FELLMAN, FRANCIS, GALIN, GOROVOY, HALL, HELMS, HENRY, HURVITZ, KAUFMAN, KOTTLER, LEWIS, LUO, MANDELL, MARCH, MARES, MCMULLEN, MITCHELL, MUNDORF, NELSON, NETLAND, OLANDER, ORENGO-NANIA, PATCHETT, PORIAS, RIPKIN, ROTHBERG, ROTBERG, SALL, SCHENKER, SEVERIN, SHARPE, SHIN, SIDOTI, SILVERSTONE, SMITH, SPADAFORA, STEWART, STEWART, STILES, TAUBER, THORNE, TINGEY, WASSERSTROM, WEISS, WEITZMAN, WILLIAMS, WALTERS, WHITSETT.

CONTINUED IN AMENDMENTS VOLUME 11

IND 51,000

AL-6221 SOLUTION
TRAVAPROST

Date Submitted: June 28, 1996

Date Approved: July 28, 1996

AMENDMENTS
VOLUME 11

1	Sep 22, 1998	SN:037	C-97-73 NEW INVESTIGATORS: HARVEY DUBINER, RICHARD LEWIS, SILVIA ORENGO-NANIA, MICHAEL ROTBERG, HOWARD SCHENKER AND ROBERT WILLIAMS.

CONTINUED IN AMENDMENTS VOLUME 12

IND 51,000

AL-6221 SOLUTION
TRAVAPROST

Date Submitted: June 28, 1996

Date Approved: July 28, 1996

AMENDMENTS
VOLUME 12

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1 Oct 13, 1998 SN:038 ANNUAL REPORT, JULY 97 TO JULY 31,98. (VOL 1 OF 2)

CONTINUED IN AMENDMENTS VOLUME 13

IND 51,000

AL-6221 SOLUTION
TRAVAPROST

Date Submitted: June 28, 1996

Date Approved: July 28, 1996

AMENDMENTS
VOLUME 13

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1 Oct 13, 1998 SN:038 ANNUAL REPORT, JULY 97 TO JULY 31,98. (VOL 2 OF 2)

CONTINUED IN AMENDMENTS VOLUME 14

IND 51,000

AL-6221 SOLUTION
TRAVAPROST

Date Submitted: June 28, 1996

Date Approved: July 28, 1996

AMENDMENTS
VOLUME 14

1	Nov 10, 1998	SN:039 C-97-72, 2 ADDITIONAL INVESTIGATORS, WIRTH & OLIVIER.
2	Dec 07, 1998	SN:040 AMENDMENT NO.2 WILL INCREASE NUMBER OF INVESTIGATIONAL SITES & REVISE STUDY ROSTER TO REFLECT ALCON EMPLOYEES. ADD H.CHOPRA & L.ROSENBERG AS NEW INVESTIGATORS.
3	Dec 16, 1998	SN:041 ADD INVESTIGATOR WILLIAM E. LARGOMARSINO.
4	Dec 18, 1998	SN:042 ADD INVESTIGATOR MARC L. WEITZMAN.
5	Feb 01, 1999	SN:043: REQUESTING SUBMISSION OF TRADENAME "TRAVATAN".
6	Mar 10, 1999	SN:044 ADDITION OF 2 CROS TO C-97-72 - PILCHER & MCNEY.
7	Mar 19, 1999	SN:045 ADDITION OF PROF.NORDMANN (FRANCE) TO C-97-77.
8	Mar 19, 1999	SN:046 NEW PROTOCOL C-98-09 IN MEXICO.
9	Mar 26, 1999	SN:047 C-97-77 FRANCE...NEW INVESTIGATORS: DENIS, BRON, LESIUR, BECHETOILLE, GEORGE, LACHKAR, FERRATON, KRETZ.
10	Apr 09, 1999	SN:048 NEW PROTOCOL C-99-08. INVESTIGATOR: DR. LAURENT.
11	Apr 21, 1999	SN:049 NEW PROTOCOL C-99-18, NEW INVESTIGATORS: J.DIETLEIN, R. HERNANDEZ, J. MONTGOMERY, AND K. SALL.

CONTINUED IN AMENDMENTS VOLUME 15

IND 51,000

AL-6221 SOLUTION
TRAVAPROST

Date Submitted: June 28, 1996

Date Approved: July 28, 1996

AMENDMENTS
VOLUME 15

1	Apr 08, 1999	REQUEST FROM FDA FOR INFORMATION ON THE MEXICO STUDY, PROTOCOL C-98-09.
2	May 18, 1999	SN:050 RESPONSE TO FDA ON MEXICO STUDY C-98-09.
3	May 24, 1999	COMMENTS RECEIVED FROM THE FDA MEDICAL REVIEWER REGARDING THE PROTOCOL.
4	Jun 09, 1999	SN:051 ADDITION OF DR. PACZKA-ZAPATA IN MEXICO.
5	Jun 09, 1999	SN:052 AMENDMENT TO PROTOCOL C-99-18 EXTENDING PHASE II OF THE STUDY BY AN ADDITIONAL TWO WEEKS.
6	Jul 07, 1999	SN:053 CHEMISTRY INFORMATION AMENDMENT: MEDIA FILLS FOR INITIAL STARTUP OF LINE D USING OVAL BOTTLE.
7	Jul 16, 1999	SN:054 AMENDMENT TO PROTOCOL C-98-09 - PRODUCT DOES NOT REQUIRE REFRIGERATION.

CONTINUED IN AMENDMENTS VOLUME 16

IND 51,000

AL-6221 SOLUTION
TRAVAPROST

Date Submitted: June 28, 1996

Date Approved: July 28, 1996

AMENDMENTS
VOLUME 16

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1 Sep 27, 1999 SN:055 VOLUME 1 OF 4 OF THE 1999 IND ANNUAL REPORT.

CONTINUED IN AMENDMENTS VOLUME 17

IND 51,000

AL-6221 SOLUTION
TRAVAPROST

Date Submitted: June 28, 1996

Date Approved: July 28, 1996

AMENDMENTS
VOLUME 17

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1 Sep 27, 1999 SN:055 VOLUME 2 OF 4 OF THE 1999 IND ANNUAL REPORT.

CONTINUED IN AMENDMENTS VOLUME 18

IND 51,000

AL-6221 SOLUTION
TRAVAPROST

Date Submitted: June 28, 1996

Date Approved: July 28, 1996

AMENDMENTS
VOLUME 18

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1 Sep 27, 1999 SN:055 VOLUME 3 OF 4 OF THE 1999 IND ANNUAL REPORT.

CONTINUED IN AMENDMENTS VOLUME 19

IND 51,000

AL-6221 SOLUTION
TRAVAPROST

Date Submitted: June 28, 1996

Date Approved: July 28, 1996

AMENDMENTS
VOLUME 19

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1 Sep 27, 1999 SN:055 VOLUME 4 OF 4 OF THE 1999 IND ANNUAL REPORT.

CONTINUED IN AMENDMENTS VOLUME 20

IND 51,000

AL-6221 SOLUTION
TRAVAPROST

Date Submitted: June 28, 1996

Date Approved: July 28, 1996

AMENDMENTS
VOLUME 20

1	Jan 14, 2000	SN:056 C-97-77 - DR. TEUS IN SPAIN, NEW INVESTIGATOR.
2	Mar 02, 2000	SN:058 EARLY DRAFT LABELING TO SUPPORT REVIEW OF TRAVATAN.
3	Feb 25, 2000	SN:057 REQUESTING SUBMISSION OF TRADENAME 'TRAVATAN`.
4	Apr 12, 2000	SN:059 NEW PROTOCOL C-99-97. PHASE I STUDY TO CHARACTERIZE THE STEADY STATE PLASMA PHARMACOKINETICS AND ITS ACID METABOLITE. ALSO, AMENDMENT #1 AND INVESTIGATOR THOMAS MARBURY. ALSO, AMENDING IND TO ADD CRO KENDRA BLEVINS TO C-97-71, C-97-72 AND C-97-73.
5	Apr 20, 2000	SN:060 REQUEST FOR PRE-NDA MEETING.
6	Apr 24, 2000	SN:061 BRIEFING PACKETS (AND ELECTRONIC COPY) FOR PRE-NDA MEETING SENT TO PUGLISI AND DOCUMENT CONTROL ROOM.

CONTINUED IN AMENDMENTS VOLUME 21

IND 51,000

AL-6221 SOLUTION
TRAVAPROST

Date Submitted: June 28, 1996

Date Approved: July 28, 1996

AMENDMENTS
VOLUME 21

1	May 19, 2000	SN:062 NEW PROTOCOL C-00-11 JAPANESE STUDY IN HAWAII. SAFETY & IOL EFFICACY.
2	May 25, 2000	SN:063 NEW PROTOCOL C-00-15 JAPANESE STUDY IN HAWAII. PHARMACOKINETIC STUDY WITH AND WITHOUT DIGITAL PUNCTAL OCCLUSION.
3	Jun 05, 2000	SN:064 NEW PROTOCOL C-00-05. PHASE I STUDY RE: URINARY EXCRETION AFTER ADMINISTRATION OF 0.004% IN SUBJECTS WITH NORMAL HEPATIC FUNCTION COMPARED TO THOSE WITH IMPAIRED.
4	Jun 22, 2000	SN:065 AMENDMENT NO.1 TO C-00-15 ADDS 3 ADDITIONAL PROCEDURES RE: THE COLLECTION OF SPECIMENS FOR TESTING.
5	Aug 02, 2000	TELEPHONE CALL FROM TONY CARRERAS. FDA INTENDS TO AUDIT 4 U.S. INVESTIGATORS. C.BEEHLER C97-71; W.PILCHARD AND R.SHIELDS C-97-72; & T.WALTERS C97-73.
6	Aug 15, 2000	SN:066 AMENDMENT #2 TO C-00-11. WILL CAPTURE FOLLOW-UP SAFETY LAB RESULTS.
7	Sep 06, 2000	SN:067 AMENDMENT 1 ADDED TO C-00-11 TO CAPTURE ADDT'L SAFETY LABORATORY PARAMETERS ON VISIT DAYS 0,3,8.

CONTINUED IN AMENDMENTS VOLUME 22

IND 51,000

AL-6221 SOLUTION
TRAVAPROST

Date Submitted: June 28, 1996

Date Approved: July 28, 1996

AMENDMENTS
VOLUME 22

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1 Sep 22, 2000 SN:068 VOLUME 1 OF 3 OF THE 2000 IND ANNUAL REPORT.

CONTINUED IN AMENDMENTS VOLUME 23

IND 51,000

AL-6221 SOLUTION
TRAVAPROST

Date Submitted: June 28, 1996

Date Approved: July 28, 1996

AMENDMENTS
VOLUME 23

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1 Sep 22, 2000 SN:068 VOLUME 2 OF 3 OF THE 2000 IND ANNUAL REPORT.

CONTINUED IN AMENDMENTS VOLUME 24

IND 51,000

AL-6221 SOLUTION
TRAVAPROST

Date Submitted: June 28, 1996

Date Approved: July 28, 1996

AMENDMENTS
VOLUME 24

---

1 Sep 22, 2000 SN:068 VOLUME 3 OF 3 OF THE 2000 IND ANNUAL REPORT.

CONTINUED IN AMENDMENTS VOLUME 25

IND 51,000

AL-6221 SOLUTION
TRAVAPROST

Date Submitted: June 28, 1996

Date Approved: July 28, 1996

AMENDMENTS
VOLUME 25

1	Dec 06, 2000	SN:069 ADDING PROTOCOL C-00-56 TO IND. SAFETY STUDY IN JAPANESE MALES IN HAWAII.
2	Jan 25, 2001	SN:070 ADDITION OF STUDY C-00-50 TO IND. PHASE III STUDY TO COMPARE THE IOP-LOWERING EFFICACY OF TRAVATAN AND XALATAN IN AFRICAN-AMERICANS WITH OAG OR OH. INVESTIGATORS: DRS. ATLAS, CALDWELL, DAY, DUBINER, MANDELL, SHARPE, STEWART, WILLIAMS.

AMENDMENTS CONTINUED IN VOLUME 26

IND 51,000

AL-6221 SOLUTION
TRAVAPROST

Date Submitted: June 28, 1996

Date Approved: July 28, 1996

AMENDMENTS
VOLUME 26

1	Feb 23, 2001	SN:071 NEW INVESTIGATORS TO C-00-50: CAMRAS, MCCURDY, OLIVIER, ORENGO-NANIA, AND SHIN.

NDA 21-257

TRAVATAN 0.0015% & 0.004% SOLUTION

Date Submitted: July 7, 2000

Date Approved:

AMENDMENTS
VOLUME 1

1	Jun 02, 2000	MEDICAL OFFICER'S COMMENTS TO SUBMISSION OF CMC.
2	Jul 12, 2000	REVIEWER AIDS (NDA ON CD'S) SUBMITTED TO PROJECT MANAGER.
3	Jul 25, 2000	REPLY TO TONY CARRERAS' REQUEST FOR INVESTIGATOR AND ENROLLMENT INFORMATION FOR PIVOTAL STUDIES.
4	Aug 04, 2000	RESPONSE TO FDA CHEMIST'S FAX OF JULY 27 AND AUGUST 1,2000.
5	Aug 08, 2000	REVIEWERS AIDS, ITEMS 5 & 6 ELECTRONIC, CROSS-LINKED CD-ROM AND MSWORD FILES.
6	Aug 10, 2000	CHEMISTRY AMENDMENT. TR'S TO PROVIDE UPDATED STABILITY DATA TO SUPPORT INITIAL 2 YEAR SHELF-LIFE. THE SECOND PART OF THIS AMENDMENT IS FILED IN AMENDMENT VOLUME 2.

CONTINUED IN AMENDMENTS VOLUME 2

NDA 21-257

TRAVATAN 0.0015% & 0.004% SOLUTION

Date Submitted: July 7, 2000

Date Approved:

AMENDMENTS
VOLUME 2

1	Aug 10, 2000	CHEMISTRY AMENDMENT. TRS TO PROVIDE UPDATED STABILITY DATA TO SUPPORT INITIAL 2-YEAR SHELF LIFE. THE FIRST HALF OF THIS AMENDMENT IS FOUND IN AMENDMENTS VOLUME 1.

CONTINUED IN AMENDMENTS VOLUME 3

NDA 21-257

TRAVATAN 0.0015% & 0.004% SOLUTION

Date Submitted: July 7, 2000

Date Approved:

AMENDMENTS
VOLUME 3

1	Aug 09, 2000	FDA CHEMIST'S CONCERNS RELATING TO STEREOCHEMISTRY ISSUES.
2	Aug 11, 2000	FDA CHEMIST'S CONCERNS RELATING TO PRODUCT STABILITY ISSUES
3	Aug 11, 2000	TELEPHONE REQUEST FROM DR. LIM FOR DATA CONCERNING BASELINE IOP FOR THE FOUR PRIMARY CLINICAL STUDIES.
4	Aug 09, 2000	PRIORITY (P) CLASSIFICATION RECEIVED.
5	Aug 17, 2000	REPLACED ITEM 5 OF NDA, TOXICOLOGY SECTION BECAUSE OF ALLEGED ILEGIBILITY, VOLUMES 19-46 OF NDA.
6	Aug 17, 2000	RESPONSE TO DR. LIM'S TELEPHONE REQUEST OF AUGUST 11.
7	Aug 22, 2000	CONCERNS RECEIVED. RANGE OF ISSUES FROM STRUCTURE ELUCIDATION TO PRODUCT MANUFACTURE.
8	Aug 22, 2000	REVIEWERS AID - PATIENT LISTINGS FROM ITEM 11 ON MS EXCEL FORMAT CD.
9	Aug 28, 2000	RESPONSE TO TONY CARRERAS'S AUGUST 2ND REQUEST FOR DATA TO SUPPORT THE FDA AUDIT OF THE CLINICAL SITE FOR 4 INVESTIGATORS IN STUDIES C-97-71 C-97-72 & C-97-73. THE SECOND HALF IS FILED IN VOLUME 4

CONTINUED IN AMENDMENTS VOLUME 4

NDA 21-257

TRAVATAN 0.0015% & 0.004% SOLUTION

Date Submitted: July 7, 2000

Date Approved:

AMENDMENTS
VOLUME 4

1	Aug 28, 2000	SECOND HALF OF THE RESPONSE TO TONY CARRERAS'S AUGUST 2ND REQUEST FOR DATA TO SUPPORT THE FDA AUDIT OF THE CLINICAL SITE FOR 4 INVESTIGATORS IN 3 STUDIES.

CONTINUED IN AMENDMENTS VOLUME 5

NDA 21-257

TRAVATAN 0.0015% & 0.004% SOLUTION

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AMENDMENTS
VOLUME 5

1	Aug 29, 2000	FDA REQUESTS CONFIRMATION THAT PACKAGE COMPATIBILITY STUDIES ARE BEING PERFORMED.
2	Aug 31, 2000	MEDICAL OFFICERS REQUEST FOR ADDITONAL INFORMATION IN CLINICAL VOLUMES.
3	Sep 05, 2000	RESPONSE TO MEDICAL OFFICERS REQUEST OF 8/31/00.
4	Sep 12, 2000	PARTIAL RESPONSES TO THE ISSUES RECEIVED IN THE AUGUST 9 LETTER.
5	Sep 14, 2000	RESPONSES TO ISSUES OF AUGUST 11 AND AUGUST 22, 2000.
6	Sep 15, 2000	RESPONSE TO ISSUES RECEIVED AUGUST 29, 2000.
7	Sep 22, 2000	TRAVOPROST LOT SUMMARY FAXED TO PHARMACOLOGY REVIEWER.
8	Sep 22, 2000	C-97-72 FOR DR. SHIELDS FAXED TO M. LEGRANGE AS REQUESTED.
9	Sep 26, 2000	FDA MEDICAL OFFICERS REQUEST FOR TABLES PRESENTED IN CLINICAL SECTION OF NDA.

CONTINUED IN AMENDMENTS VOLUME 6

NDA 21-257

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AMENDMENTS
VOLUME 6

1	Sep 26, 2000	PACKAGING SYSTEM TO BE USED AS REVIEWERS AID PROVIDED AS REQUESTED.
2	Oct 02, 2000	RESPONSE TO THE 9/26/2000 COMMENTS RECEIVED FROM MEDICAL REVIEWER TO DR. CHAMBERS. ELECTRONIC VERSION OF RESPONSE SENT TO MIKE PUGLISI.
3	Oct 19, 2000	OUTSTANDING RESPONSES TO ISSUES 6, 7 & 8 OF COMMENTS RECEIVED IN THE AUGUST 9 FAX.
4	Oct 24, 2000	RESPONSES TO INFORMATION REQUESTED BY CHEMISTRY REVIEWER CONCERNING STABILITY OF THE NON-OVERWRAPPED BOTTLE.

CONTINUED IN AMENDMENTS VOLUME 7

NDA 21-257

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AMENDMENTS
VOLUME 7

1	Oct 27, 2000	COMMENTS FROM FENSELAU CONCERNING REVIEWER RECOMMENDED SPECIFICATIONS FOR DRUG SUBSTANCE AND DRUG PRODUCT.
2	Nov 06, 2000	RESPONSE TO INFORMATION REQUESTED BY CHEMISTRY REVIEWER DATED MAY 15, 2000.
3	Nov 06, 2000	120 DAY SAFETY UPDATE. (CD AND HARD COPY)

CONTINUED IN AMENDMENTS VOLUME 8

NDA 21-257

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AMENDMENTS
VOLUME 8

1	Nov 14, 2000	REQUEST FROM FDA MEDICAL OFFICER RE: 120-DAY SAFETY UPDATE.
2	Nov 14, 2000	INFORMATION REQUESTED FROM FDA CHEMISTRY REVIEWER.
3	Nov 17, 2000	RESPONSE TO CHEMISTRY REVIEWERS COMMENTS OF 11/14/00.
4	Nov 21, 2000	RESPONSE TO MEDICAL OFFICERS REQUEST OF 11/14/00.
5	Dec 08, 2000	COPY OF REVISED DRAFT LABELING RECEIVED FROM FDA. 15 DEFICIENCIES ALSO RECEIVED.
6	Dec 11, 2000	RESPONSE TO FDA REQUEST FOR ENVIRONMENTAL ASSESSMENT. (RESULT OF TELEPHONE REQUEST).
7	Dec 18, 2000	FDA PHARM/TOX REVISIONS TO DRAFT PACKAGE INSERT FAXED TO ALCON 12/8.
8	Dec 22, 2000	RECEIPT OF APPROVABLE (ACTION) LETTER WITH ISSUES AND COMMENTS, FROM FDA.
9	Dec 27, 2000	MEDIA FILL DATA REQUESTED BY FDA (DR. COONEY). THIS DATA WAS ALSO FILED WITH THE FDA DALLAS OFFICE.
10	Dec 27, 2000	PROPOSED REVISED PACKAGE INSERT FILED TO NDA.

X
X
X
X AMENDMENTS CONTINUED IN VOLUME 9

NDA 21-257

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AMENDMENTS
VOLUME 9

1	Dec 26, 2000	RESPONSE TO FDA APPROVABLE (ACTION) LETTER OF 12/22/00. TOTAL OF 16 VOLUMES. BEGINNING WITH "AMENDMENTS VOLUME 9" AND CONTINUING THROUGH "AMENDMENTS VOLUME 24".

NDA 21-257

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AMENDMENTS
VOLUME 10

1	Dec 26, 2000	RESPONSE TO FDA APPROVABLE (ACTION) LETTER OF 12/22/00. TOTAL OF 16 VOLUMES. BEGINNING WITH "AMENDMENTS VOLUME 9" AND CONTINUING THROUGH "AMENDMENTS VOLUME 24".

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		AMENDMENTS VOLUME 11
1	Dec 26, 2000	RESPONSE TO FDA APPROVABLE (ACTION) LETTER OF 12/22/00. TOTAL OF 16 VOLUMES. BEGINNING WITH "AMENDMENTS VOLUME 9" AND CONTINUING THROUGH "AMENDMENTS VOLUME 24".

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AMENDMENTS
VOLUME 12

1	Dec 26, 2000	RESPONSE TO FDA APPROVABLE (ACTION) LETTER OF 12/22/00. TOTAL OF 16 VOLUMES. BEGINNING WITH "AMENDMENTS VOLUME 9" AND CONTINUING THROUGH "AMENDMENTS VOLUME 24".

NDA 21-257

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AMENDMENTS
VOLUME 13

1	Dec 26, 2000	RESPONSE TO FDA APPROVABLE (ACTION) LETTER OF 12/22/00. TOTAL OF 16 VOLUMES. BEGINNING WITH "AMENDMENTS VOLUME 9" AND CONTINUING THROUGH "AMENDMENTS VOLUME 24".

NDA 21-257

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AMENDMENTS
VOLUME 14

1	Dec 26, 2000	RESPONSE TO FDA APPROVABLE (ACTION) LETTER OF 12/22/00. TOTAL OF 16 VOLUMES. BEGINNING WITH "AMENDMENTS VOLUME 9" AND CONTINUING THROUGH "AMENDMENTS VOLUME 24".

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AMENDMENTS
VOLUME 15

1	Dec 26, 2000	RESPONSE TO FDA APPROVABLE (ACTION) LETTER OF 12/22/00. TOTAL OF 16 VOLUMES. BEGINNING WITH "AMENDMENTS VOLUME 9" AND CONTINUING THROUGH "AMENDMENTS VOLUME 24".

NDA 21-257

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AMENDMENTS
VOLUME 16

1	Dec 26, 2000	RESPONSE TO FDA APPROVABLE (ACTION) LETTER OF 12/22/00. TOTAL OF 16 VOLUMES. BEGINNING WITH "AMENDMENTS VOLUME 9" AND CONTINUING THROUGH "AMENDMENTS VOLUME 24".

NDA 21-257

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		AMENDMENTS VOLUME 17
1	Dec 26, 2000	RESPONSE TO FDA APPROVABLE (ACTION) LETTER OF 12/22/00. TOTAL OF 16 VOLUMES. BEGINNING WITH "AMENDMENTS VOLUME 9" AND CONTINUING THROUGH "AMENDMENTS VOLUME 24".

NDA 21-257

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AMENDMENTS VOLUME 18		
1	Dec 26, 2000	RESPONSE TO FDA APPROVABLE (ACTION) LETTER OF 12/22/00. TOTAL OF 16 VOLUMES. BEGINNING WITH "AMENDMENTS VOLUME 9" AND CONTINUING THROUGH "AMENDMENTS VOLUME 24".

NDA 21-257

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Date Submitted: July 7, 2000

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AMENDMENTS
VOLUME 19

1	Dec 26, 2000	RESPONSE TO FDA APPROVABLE (ACTION) LETTER OF 12/22/00. TOTAL OF 16 VOLUMES. BEGINNING AT "AMENDMENTS VOLUME 9" AND CONTINUING THROUGH "AMENDMENTS VOLUME 24".

NDA 21-257

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AMENDMENTS
VOLUME 20

1	Dec 26, 2000	RESPONSE TO FDA APPROVABLE (ACTION) LETTER OF 12/22/00. TOTAL OF 16 VOLUMES. BEGINNING WITH "AMENDMENTS VOLUME 9" AND CONTINUES THROUGH AMENDMENTS.VOLUME 24".

NDA 21-257

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AMENDMENTS
VOLUME 21

1	Dec 26, 2000	RESPONSE TO FDA APPROVABLE (ACTION) LETTER OF 12/22/00. TOTAL OF 16 VOLUMES. BEGINNING WITH "AMENDMENTS VOLUME 9" AND CONTINUING THROUGH "AMENDMENTS VOLUME 24".

NDA 21-257

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AMENDMENTS
VOLUME 22

1	Dec 26, 2000	RESPONSE TO FDA APPROVABLE (ACTION) LETTER OF 12/22/00. TOTAL OF 16 VOLUMES. BEGINNING WITH "AMENDMENTS VOLUME 9" AND CONTINUING THROUGH "AMENDMENTS VOLUME 24".

NDA 21-257

TRAVATAN 0.0015% & 0.004% SOLUTION

Date Submitted: July 7, 2000

Date Approved:

		AMENDMENTS VOLUME 23
1	Dec 26, 2000	RESPONSE TO FDA APPROVABLE (ACTION) LETTER OF 12/22/00. TOTAL OF 16 VOLUMES. BEGINNING WITH "AMENDMENTS VOLUME 9", AND CONTINUING THROUGH "AMENDMENTS VOLUME 24".

NDA 21-257

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AMENDMENTS
VOLUME 24

1	Dec 26, 2000	RESPONSE TO FDA APPROVABLE (ACTION) LETTER OF 12/22/00. TOTAL OF 16 VOLUMES. BEGINNING WITH "AMENDMENTS VOLUME 9", AND CONTINUING THROUGH "AMENDMENTS VOLUME 24".

NDA 21-257

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AMENDMENTS
VOLUME 25

1	Jan 04, 2001	FILING OF REVISED CARTON, FOIL OVERWRAP & CONTAINER LABELING. INCLUDES CD-ROM.
2	Jan 11, 2001	REVISED DRAFT CARTON, FOIL OVERWRAP AND CONTAINER LABELS E-MAILED TO M. PUGLISI.
3	Jan 12, 2001	REVISED DRAFTS FOR CARTON, LABEL, AND FOIL OVERWRAP WITH REVISED FONTS E-MAILED TO M. PUGLISI.
4	Jan 17, 2001	REVISED CARTON, FOIL OVERWRAP AND CONTAINER LABELING FOR BOTH TRADE & PROFESSIONAL SAMPLE PRODUCT FILED. THIS LABELING WAS AGREED UPON ON JANUARY 12, 2001.
5	Jan 25, 2001	REQUESTS FOR ADDITIONAL INFORMATION FROM MEDICAL OFFICER.
6	Jan 25, 2001	FAXED PAGES FROM THE NDA INTEGRATED SUMMARY OF EFFICACY REQUESTED BY THE FDA.
7	Jan 30, 2001	REQUEST FROM FDA FOR THE TEST PROCEDURE THAT IS TO BE FOLLOWED BY THE ANALYST DURING DRUG SUBSTANCE TESTING.
8	Feb 01, 2001	RESPONSE TO FDA CHEMISTRY REVIEWER'S COMMENTS OF JAN.30.
9	Feb 01, 2001	RESPONSE TO FDA MEDICAL REVIEWERS COMMENTS OF JAN.25,2001.

AMENDMENTS ARE CONTINUED IN VOLUME 26

NDA 21-257

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AMENDMENTS
VOLUME 26

1	Feb 06, 2001	COMMENTS RECEIVED FROM CHEMISTRY REVIEWER.
2	Feb 07, 2001	COMMENTS RECEIVED FROM CHEMISTRY REVIEWER.
3	Feb 07, 2001	REQUEST FROM MEDICAL OFFICER.
4	Feb 09, 2001	RESPONSE TO CHEMISTRY REVIEWERS COMMENTS OF FEBRUARY 6.
5	Feb 12, 2001	REPLY TO MEDICAL OFFICERS REQUEST OF FEBRUARY 7TH.
6	Feb 14, 2001	REVISED PACKAGE INSERT RECEIVED FROM PUGLISI.
7	Feb 15, 2001	REVISION TO FDA'S PROPOSED DRAFT P.I. OF FEBRUARY 14TH.
8	Feb 16, 2001	RESPONSE TO FEB. 7TH CHEMISTRY REVIEWERS COMMENTS.

AMENDMENTS CONTINUED IN VOLUME 27

NDA 21-257

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AMENDMENTS
VOLUME 27

1	Feb 19, 2001	REQUEST TO CHAMBERS/RUMBLE FOR COMMENT ON DRAFT LABELING PIECES.
2	Feb 22, 2001	REQUEST FROM FDA CHEMISTRY REVIEWER TO CONFIRM SPECS FOR DRUG SUBSTANCE. TELECONFERENCE MADE TO DR. FENSELAU & NG. ALCON PARTICIPANTS: KRUEGER, DAGNON, DUNN, BELL, FISCHER, NUGENT, KABRA & GAN.
3	Feb 26, 2001	FAX TO PUGLISI: DRAFT RESPONSE TO THE 2/22/01 REQUEST RECEIVED FROM THE CHEMISTRY REVIEWER.
4	Feb 27, 2001	REQUEST FROM FDA CHEMISTRY REVIEWER TO CONFIRM SPECS FOR DRUG PRODUCT.
5	Feb 28, 2001	REVISED SPECIFICATION PAGE TO REFLECT THE AGREEMENT REACHED 2/28/01 WITH DR. FENSELAU.
6	Feb 28, 2001	RESPONSE TO CHEMISTRY REVIEWERS COMMENTS OF 2/22 AND 2/27.
7	Feb 28, 2001	FINAL DRAFT INSERT TEXT AND RED-LINED VERSION REFLECTING CHANGES FROM FEB. 15TH VERSION.
8	Mar 01, 2001	REVISED FINAL DRAFT PACKAGE INSERT.
9	Mar 09, 2001	FINAL CHEMISTRY VALIDATION PACKAGE REQUESTED BY REVIEW CHEMIST ON 2/22/2001. [NOTE: THIS RESPONSE IS LARGE AND DIVIDED INTO 3 BINDERS. THIS IS THE FIRST PART.]

AMENDMENTS ARE CONTINUED IN VOLUME 28

NDA 21-257

TRAVATAN 0.0015% & 0.004% SOLUTION

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AMENDMENTS
VOLUME 28

1	Mar 09, 2001	FINAL CHEMISTRY VALIDATION PACKAGE REQUESTED BY REVIEW CHEMIST ON 2/22/2001. [NOTE: THIS IS THE SECOND OF THREE PARTS OF THIS LARGE RESPONSE.]

AMENDMENTS ARE CONTINUED IN VOLUME 29

NDA 21-257

TRAVATAN 0.0015% & 0.004% SOLUTION

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AMENDMENTS
VOLUME 29

1	Mar 09, 2001	FINAL CHEMISTRY VALIDATION PACKAGE REQUESTED BY REVIEW CHEMIST ON 2/22/2001. [NOTE: THIS IS THE THIRD OF THREE PARTS OF THIS LARGE RESPONSE.]
2	Mar 16, 2001	TRAVATAN APPROVAL LETTER ! (8 MONTHS, 1 WEEK)
3	Mar 20, 2001	20 COPIES OF FPL TO FDA AS REQUESTED IN 3/16/01 APPROVAL LETTER.

CONTINUED IN SUPPLEMENTS VOLUME 1